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(54) Title: SUBSATURATED TRANSDERMAL DRUG DELIVERY DEVICE EXHIBITING ENHANCED DRUG FLUX

(57) Abstract

Transdermal administration of hydrophobic drugs via a diffusion mechanism in which the drug is dissolved in a carrier at concentrations that are 10 % to 80 % of the saturation concentration. The flux of drug from the device is non-Fickian and is substantially greater than the flux observed when the drug is at saturation.

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SUBSATURATED TRANSDERMAL DRUG DELIVERY DEVICE EXHIBITING ENHANCED DRUG FLUX

Description

Technical Field

This invention is in the field of transdermal drug administration. More particularly it relates to a device and method that provides the drug at unexpectedly high flux.

Background

Transdermal drug delivery devices typically comprise a drug reservoir composed of the drug and a carrier from which the drug is released by diffusion. Examples of such devices are described in "Transdermal Drug Delivery Systems," U.S. Pharmacist, pp. 49-78.

Fick's Law has classically been used to characterize the drug release kinetics of such diffusional devices. According to this law the maximum flux of drug from such a device occurs when the concentration of drug in the carrier is at saturation. Correlatively, the art teaches that the maximum flux of the drug across skin (when the skin is not a rate controlling barrier to the drug) from a given drug-carrier combination also occurs when the concentration of drug in the carrier is at saturation. Since maximum skin flux is desired with most drugs, diffusional devices have traditionally been designed to maintain saturation conditions in the carrier over the dispensing lifetime of the device.

Applicants have now unexpectedly discovered that the maximum skin flux from diffusional devices in which the drug is hydrophobic occurs when the drug is maintained below saturation in the carrier. This finding is totally contrary to the conventional wisdom followed in the transdermal drug device art. Further, applicants have employed this discovery to permit testosterone to be delivered across nonscrotal skin at therapeutically effective levels. As discussed in detail below, the art teaches that effective transdermal delivery of testosterone can only be achieved through scrotal skin.

Some prior patents have suggested in passing that while it is desirable to maintain the concentration of drug at saturation because maximum flux occurs there at, that the drug concentration could be below saturation. See for instance U.S. Pats. Nos. 4,568,343; 4,645,502; 4,816,258; 4,863,738; 4,865,848; and 4,908,027. These patents, however, fail to suggest maintenance of subsaturation levels of drug throughout the dispensing lifetime or that any increase in skin flux could be achieved with hydrophobic drugs under such conditions.

Testosterone therapy is currently indicated for treatment of male hypogonadism, anemia, breast cancer, and hereditary angioedema. It is also being considered for treating a variety of other conditions such as male osteoporosis that appear to be mediated by androgen deficiency. Traditional modalities for administering testosterone have included: intramuscular injection of long-acting testosterone esters such as the enanthate because testosterone itself is rapidly degraded by the liver if administered orally; oral administration of testosterone undecanoate, which provides systemically available testosterone; and subcutaneous implantation of

fused testosterone pellets. None of these traditional modalities provides totally physiological levels or circadian patterns of testosterone and its active metabolites, dihydrotestosterone (DHT) and estradiol (E_2).

It is known that steroids, including testosterone, are absorbed through skin. However, the permeability to testosterone of skin areas that are normally used for transdermal delivery (e.g., the neck, back, chest, arms) is too low to permit delivery of the amounts of testosterone needed for therapy (typically 5-10 mg/day) through a limited area of skin. In this regard, Korennan, S.G., et al., (Am J Med (1987) 83:471-478) in an article on testosterone delivery for treating hypogonadism concluded "a more permeable skin area with a much higher absorption rate was required to provide programmed transdermal delivery to a limited area." This led Korennan et al. to select scrotal skin--which is highly permeable to testosterone--as a site for testosterone delivery. The article further describes a transscrotal delivery system developed by ALZA Corporation. U.S. 4,704,282 describes that system in detail. It consists of a polymer matrix that contains testosterone at subsaturation levels and a fabric reinforcement incorporated into the matrix that also is a limited solvent for testosterone. The patent indicates that a subsaturated matrix is used because a declining testosterone release rate is desired. The reinforcing fabric, in addition to providing a structural support function, is said to act as a secondary reservoir for testosterone which has the effect of flattening the release rate profile (see Figure 2 of the patent). While the patent states that permeation enhancers may be present in the matrix, no examples of the use of such enhancers are described. The patent gives no data on the

skin flux of testosterone provided by its systems. Example 2 of the patent states that its system may be applied to nonscrotal skin, particularly the thigh, to produce "similar results" as when applied to scrotal skin. This statement is, however, contradicted by the later Korennan et al. article (which also originates from ALZA Corporation) which reports that systems applied to the thigh did not give increased blood levels of testosterone.

Ahmed, S.R., et al. (J Clin Endocrinol Metab (1988) 66:546-557) and Findlay, J.C. (J Clin Endocrinol Metab (1989) 68:369-373) report that the 60 cm^2 ALZA transscrotal system delivers about 3.7 mg/day and produces low-normal testosterone levels in hypogonadal men. Such dosages are believed to be somewhat less than the amount needed to mimic endogenous production (5-10 mg/day). Furthermore, since scrotal skin has a relatively high level of 5α-reductase, continuous transscrotal delivery of testosterone produces levels of DHT and DHT/testosterone ratios 4- to 5-fold greater than normal. Such abnormal levels and ratios may give rise to undesirable side effects.

In sum, the art teaches away from transdermally administering testosterone through nonscrotal skin because of the low permeability of such skin to testosterone. Transscrotal delivery of testosterone is taught, but such delivery is associated with high DHT and DHT/testosterone ratio levels and does not provide a level of testosterone delivery that mimics endogenous production. Further, scrotal skin is sensitive and limited in area, which may result in discomfort and poor patient acceptance of this modality of delivery.

Disclosure of the Invention

As described above, the invention is based on the discovery that in the case of transdermal administration of hydrophobic drugs from a diffusional device, maximum skin flux is achieved at concentrations of drug in the carrier that are below saturation. In some instances the increase in flux at subsaturation is dramatically higher than at saturation. The invention thus takes the form of devices for and methods of administering hydrophobic drugs transdermally that are based on this finding.

Accordingly, in one aspect, the invention is a device for administering by diffusion a hydrophobic drug transdermally to a patient for a prolonged time period comprising:

(a) a reservoir comprising the drug dissolved in a carrier, the amount and solubility of the drug in the carrier defining a condition of subsaturation that is sufficient to provide a drug skin flux substantially throughout said time period that is significantly greater than the drug skin flux provided when the carrier is saturated with drug; and

(b) means for maintaining the reservoir in drug delivery communication with the skin of the patient.

In another aspect the invention is an improvement in the method for administering a hydrophobic drug transdermally to a patient for a prolonged time period by placing a reservoir comprising the drug dissolved in a carrier in communication with the skin of the patient which improvement comprises having the concentration of the drug in the carrier below saturation at the start of the period and maintaining subsaturation thereafter for a sufficient time to provide substantially throughout the time period a drug skin flux that is

substantially greater than the drug skin flux provided when the carrier is saturated with the drug.

Another aspect of the invention is a method of increasing the flux of a hydrophobic drug from a reservoir of the drug dissolved in a carrier that is in drug delivery communication with an area of unbroken skin of a patient for a prolonged time period above the flux provided when the concentration of drug in the carrier is at saturation comprising having the concentration of drug in the carrier at below saturation at the start of the period and maintaining subsaturation thereafter for a time sufficient to provide said increase substantially throughout the time period.

Still another aspect of the invention is a device for administering testosterone transdermally across an area of unbroken nonscrotal skin at a flux from 5 to 30 $\mu g/cm^2/hr$ comprising:

(a) a reservoir comprising testosterone dissolved in a carrier, and a skin permeation enhancer, the amount and solubility of testosterone in the carrier defining a condition of subsaturation that causes enhanced permeation of testosterone through nonscrotal skin and wherein the combined permeation enhancement resulting from said condition of subsaturation and said permeation enhancer provide said flux; and

(b) means for maintaining the reservoir in diffusional communication with said area of unbroken nonscrotal skin.

Brief Description of the Drawings

Figures 1 and 2 are graphs of the results of the tests described in Example 9.

Figures 3 and 4 are bar graphs comparing the results of the tests described in Example 9 with the prior art.

Figures 5 and 6 are graphs of the test results of Example 10.

Figures 7, 8 and 9 are graphs of data described in Example 10.

Modes for Carrying Out the Invention

The term "drug" as used to describe the principal active ingredient of the invention device intends a biologically active compound or mixture of compounds that has a therapeutic, prophylactic and/or physiological effect on the wearer of the device. Examples of the types of drugs that may be used in the device are antiinflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, antidepressants, antipsychotic drugs, tranquilizers, antianxiety drugs, narcotic antagonists, antiparkinsonism agents, cholinergic agonists, anticancer drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistamines, antimigrane agents, vasodilators, hormonal agents, contraceptive agents, diuretics, antihypertensive agents, cardiovascular drugs, and the like.

As used herein the term "hydrophobic" intends that the solubility of the drug in water at room temperature is <50 μg/ml. Specific examples of hydrophobic drugs are steroids such as estrogens, progestogens, testosterone, norgestrel, norethindrone acetate and medroxyprogesterone acetate.

The phrase "prolonged time period" means a period of at least about one day, usually 1-14 days, more

usually 1-7 days. The term "substantially throughout" intends at least about 60% of the time period, more usually at least 80%, and preferably 100% of the period.

The term "skin flux" intends the rate of transfer of drug across skin as measured by the method of Merritt and Cooper (J Controlled Release (1984) 1:161). The units of flux are preferably $\mu g/cm^2/hr$.

The term "significantly greater" that is used to characterize the increase in skin flux achieved through use of the invention will typically denote an increase in skin flux of at least about 25%, usually 25% to 400%, and more usually 50% to 200% over the skin flux provided when the carrier is saturated with the drug.

The term "nonscrotal skin" means human skin excepting the skin of the male human genitalia. It will normally denote the skin of relatively hair-free portions of the body such as the limbs, back, chest, buttocks, hips, and neck.

As used here, the term "testosterone therapy" intends treatment of any indication for which testosterone is indicated, including, without limitation, primary, secondary and other male hypogonadal states in adults and adolescents, anemia, hereditary angioedema, male contraception, male infertility disorders, post-surgical recovery, male impotence, hormone replacement in elderly males, and hypogonadal states associated with AIDS. Primary (testicular) hypogonadism disorders include Klinefelder's Syndrome, viral orchitis, and low testosterone production caused by trauma, radiation or chemotherapy, or alcohol abuse. Secondary (hypothalamic/pituitary) disorders include those associated with hypothalamic hypogonadism, suprasellar tumors, and pituitary tumors. Other male hypogonadism

disorders include those associated with aging, systemic illnesses, stress, and diabetes mellitus.

The phrase "corresponds substantially to endogenous blood levels produced by healthy young adult male humans" intends a blood level profile that closely approximates the circadian rhythm of testosterone production shown in Figure 7 of the drawings.

The devices of the invention release drug continuously by diffusion. In this mode, the driving force is the difference in drug concentration between the device reservoir and the skin and underlying tissue. The drug, which is entirely dissolved in the carrier or vehicle in the case of the present invention, permeates through the carrier to the skin. The carrier is, of course, in drug delivery (diffusional) communication with the skin--which means that it either contacts the skin directly or contacts material interposed between the carrier and the skin that provides a permeation pathway for the drug and, if present, permeation enhancer, to migrate from the reservoir to the skin. The interposed material may be homogeneous, heterogeneous, or be composed of a multiplicity of distinct layers. In any event the interposed material is permeable to the drug and preferably is not a rate-controlling barrier to diffusion (i.e., it is at least as permeable to the drug, and, if present, permeation enhancer, as the carrier).

As indicated above, the carrier or vehicle is permeable to drug. In this regard the diffusion coefficient of the drug in the carrier will usually be between 1×10^{-6} and 1×10^{-12} cm^2/sec, more usually between 1×10^{-7} and 1×10^{-10} cm^2/sec. The solubility of the drug in the carrier should be such that sufficient drug is contained in the device to provide the required cumulative dose of drug, which will vary from drug to

drug. At the same time, the solubility should not be so low as to require the device to be impractically large in area or thickness. In most instances, the solubility of drug in the carrier will be in the range of 1 to 500 mg/ml, more usually 1 to 200 mg/ml (measured at room temperature). The amount of drug in the carrier will normally range between 0.001 and 100 mg, more usually between 1 and 50 mg. The thickness of the reservoir will usually be about 0.01 to 5 mm, more usually 0.03 to 2 mm. The area of the device in drug delivery (diffusional) contact with the skin will usually be between about 1 and 150 cm^2, more usually between 5 and 40 cm^2.

In the case of testosterone, its solubility in the carrier should be such that sufficient testosterone is contained in the device to provide the required cumulative dose of testosterone, which will normally be in the range of 5 to 10 mg/day. At the same time, the solubility should not be so low as to require the device to be impractically large in area or thickness. The amount of testosterone in the carrier will normally range between 5 and 50 mg per unit dosage form, more usually between 10 and 20 mg. The thickness of the reservoir will usually be about 0.01 to 5 mm, more usually 0.03 to 2 mm.

The carrier may be a solid or semi-solid polymer that enables the device to be a "solid-state" device (i.e., no liquid component at room temperature). Alternatively, the carrier may be in a fluid form (e.g., liquid, gel, emulsion, suspension, and be aqueous or nonaqueous. Examples of fluid carriers that may be used are alcohols such as ethanol, alcohol-water mixtures, and low molecular weight polymers such as polyethylene glycol. Examples of solid polymeric carriers that may be used in this invention are polyacrylates,

polymethacrylates, silicone polymers, polyalkyloxides, natural and synthetic rubbers and the dermatologically acceptable adhesives described in U.S. 3,934,097.

In the case of testosterone, the carrier is preferably a fluid. Examples of fluid carriers that may be used are alcohols such as ethanol, alcohol-water mixtures, and low molecular weight polymers such as polyethylene glycol. Ethanol is preferred and also provides permeation enhancement. In the case of ethanol, the carrier normally constitutes 20% to 70% by volume of the reservoir, more usually 40% to 60%, and preferably approximately 50%. Alternatively, the carrier may be a solid or semisolid matrix suxh as a pressure-sensitive adhesive.

The concentration of drug in the carrier will usually be between 10% and 80% of saturation concentration, usually 15% and 60% of saturation substantially throughout the administration period. Depending upon the nature of the carrier and other components of the reservoir (permeation enhancers), the concentration of drug relative to saturation may decrease or increase over the administration period. If the solubility of the drug in the carrier (whether modified or not by other components) remains constant over the period, the concentration relative to saturation will decrease. On the other hand, if the solubility decreases (for instance, through delivery of a permeation enhancer that also increases solubility), then the concentration relative to saturation will increase.

A permeation enhancer may be administered concurrently with the drug in order to further increase the skin flux of drug across the skin. For testosterone, an enhancer is necessary. The enhancer may also be contained within the reservoir or be administered from a

separate reservoir underlying or overlying the drug reservoir. For design simplicity, when used, the enhancer will preferably be contained in the drug reservoir. Aside from the requirements that the enhancer be compatible with the drug and carrier, there are no limitations on the enhancers that may be used in the invention. Examples of enhancers known in the art are those described in U.S. Pats. Nos. 3,989,816; 4,316,893; 4,863,970; 4,764,379; 4,537,776; and EPA (Pub. No.) 272,987, the disclosures of which, as they relate to enhancers, are incorporated herein by reference. A preferred enhancer for use with testosterone is a mixture of ethanol (also carrier), glycerol monooleate (GMO) and methyl laurate (ML). The amounts of each of GMO and ML in the reservoir will normally be 0.5% to 5% by volume, preferably approximately 2.5%. The amount of ethanol will be that previously described. The reservoir may also contain amounts of other materials such as gelling agents and antiirritants. Glycerin is a preferred antiirritant and may be present at 5% to 50%, preferably 20% to 30% by volume. The use of glycerin as an anti-irritant is described in U.S. 4,855,294.

The skin testosterone flux provided by the invention is about 5 to 30 $\mu g/cm^2/hr$, and preferably about 10 to 20 $\mu g/cm^2/hr$. In contrast, the testosterone skin flux provided by conventional transdermal administration is typically less than 0.5 $\mu g/cm^2/hr$. The high skin fluxes realized through the invention are a result of enhancement due to the subsaturation concentration of testosterone in the carrier and the enhancement due to the permeation enhancer.

For treating male hypogonadism it is desired to provide daily administration in a 24-hr release rate profile that mimics the endogenous diurnal testosterone

production pattern. This in turn leads to a circadian rhythm in testosterone levels. Figure 7 of the drawings (open circles) shows a representative circadian rhythm of testosterone production over a one-day period. As shown, testosterone levels peak in the early morning hours and then decline to trough values in the evening.

The device of the invention may be embodied in various types of structures known in the transdermal drug delivery art. For instance, the drug reservoir, which is the most important component of the device, may comprise a simple matrix of a subsaturated solution of the drug in the carrier or be in the form of a fibrous body impregnated with the subsaturated solution of drug in the carrier. In addition to the reservoir, the device includes means for maintaining the reservoir in drug-delivery communication with the skin. Such means include a carrier which is also an adhesive, a separate basal adhesive layer underlying the reservoir, a peripheral ring of adhesive that is interconnected to the reservoir, an adhesive overlay for the reservoir, and straps. Preferably the means is either an adhesive carrier or a separate underlying adhesive layer. Preferably the device is in the form of a laminated composite.

In addition to the reservoir and affixation means, the device may further include a backing that overlies the reservoir and protects the reservoir and/or prevents back-diffusion of drug from the reservoir, one or more structural layers to provide the device with appropriate mechanical properties, and/or a release liner layer that underlies the reservoir and which is removed prior to use.

These devices may be manufactured by conventional techniques used in the transdermal drug delivery device art. For instance the drug and carrier

may be mixed in the desired proportions to form a homogeneous mix and cast or otherwise applied to a backing layer, followed by lamination to a release liner layer. If a separate basal adhesive layer is desired, it may be cast onto the release liner layer prior to such lamination. As indicated above, the solubility of drug in the carrier and the size (thickness of reservoir and area in drug delivery communication with the skin) are chosen to maintain subsaturation in the reservoir over the desired dispensing lifetime of the device and provide the necessary cumulative dose of drug.

The following examples further illustrate the invention and its unique characteristics. These examples are not intended to limit the invention in any manner. In the following examples in vitro steady state transdermal flux across human cadaver skin was determined using the method of Merritt and Cooper, supra. Unless otherwise indicated percentages and proportions are by volume.

Example 1

Formulations of progesterone at varying concentrations were made by mixing progesterone with the indicated ingredients and applied to cadaver skin. The transdermal fluxes for these formulations are reported in Table 1 below. The meanings of the abbreviations that appear in the table are: Gly = glycerine; GDO = glycerol dioleate; ML = methyl laurate; OA = oleic acid; GMO = glycerol monooleate.

Table 1

Enhancer Systems*	Progesterone Conc. (mg/ml)	N	Flux ($\mu g/cm^2/hr$)
1. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GDO/ML/OA	75.0	8	2.12 ± 0.47
2. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GDO/ML/OA	50	18	4.51 ± 1.37
3. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GDO/ML/OA	25	3	5.52 ± 1.38
4. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	75	8	3.35 ± 2.18
5. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	50	18	7.63 ± 3.00
6. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	37.5	6	8.18 ± 0.90
7. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	25	18	6.37 ± 1.88
8. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	10	3	1.84 ± 0.33

* Systems #1 - #8 were gelled by adding 2.5% (w/v) Carbopol 1342, pHs were unadjusted (3.2 - 3.5) and the loading doses were 0.075 ml.

In Table 1, systems 1 and 4 contain progesterone at saturation. Systems 1-3 are alike except for progesterone concentration, and systems 4-8 are alike

except for progesterone concentration. The two sets of systems are alike except that one (1-3) contains GDO and the other (4-8) contains GMO. As shown by the flux data in Table 1, the flux is significantly greater in those systems (except 8) in which the progesterone is at subsaturated concentrations (systems 1, 3, 5-7) than when the progesterone is at saturation.

Example 2

Additional progesterone systems were formulated and tested as in Example 1. The results of these tests are shown in Table 2 below. Abbreviations are as in Example 1. Progesterone was present at saturation in system 1 and below saturation in systems 2-6.

Table 2

Enhancer Systems*	Progesterone Conc. (mg/ml)	N	Flux, ($\mu g/cm^2/hr$)
1. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GDO/ML/OA	50	12	6.01 ± 1.73
2. 60/28/10/1/1 EtOH/H_2O/Gly/GMO/ML	30	3	13.03 ± 3.35
3. 60/28/10/1/1 EtOH/H_2O/Gly/GMO/ML	25	3	12.98 ± 2.06
4. 60/28/10/1/1 EtOH/H_2O/Gly/GMO/ML	20	9	15.89 ± 6.81
5. 60/28/10/1/1 EtOH/H_2O/Gly/GMO/ML	15	12	13.13 ± 1.87
6. 60/28/10/1/1/1 EtOH/H_2O/Gly/GMO/ML	10	5	11.13 ± 1.98

* Systems were gelled by adding 2.5% (w/v) Carbopol 1342 and the loading doses were 0.075 ml.

As in Example 1, the fluxes of progesterone at concentrations below saturation were significantly greater than at saturation.

Example 3

This Example shows that the phenomenon of higher drug flux at subsaturation unexpectedly occurs only with hydrophobic drugs.

Formulations of the hydrophilic drugs oxybutynin HCl and mecamylamine HCl were prepared and tested as in Examples 1 and 2. Tables 3 and 4 below report the results of those tests. The formulations of Table 3 containing oxybutynin HCl at 40 mg/ml were saturated and the formulations of Table 4 containing 80 mg/ml of mecamylamine HCl were saturated. All other systems were at drug concentrations below saturation.

Table 3

Enhancer Systems	Oxybutyrin Conc. (mg/ml)	N	Flux ($\mu g/cm^2/hr$)
1. 40/53/5/2 EtOH/H_2O/Gly/GMO	40	4	29.1 ± 11.2
	20	12	16.9 ± 5.2
	10	6	13.3 ± 2.6
	5	3	5.6 ± 0.9
2. 40/54/5/1 EtOH/H_2O/Gly/GMO	40	5	38.8 ± 18.9
	20	12	17.5 ± 5.1
	10	6	10.1 ± 3.3
	5	3	8.0 ± 1.4
3. 30/63/5/2 EtOH/H_2O/Gly/GMO	40	6	23.9 ± 10.0
	20	12	14.8 ± 6.1
	10	9	8.3 ± 3.8
	5	3	2.2 ± 0.2
4. 30/64/5/1 EtOH/H_2O/Gly/GMO	40	6	27.5 ± 13.1
	20	15	13.6 ± 5.2
	10	6	5.4 ± 2.5
	5	3	1.7 ± 0.3

Table 4

Enhancer Systems	Mecamylamine Conc. (mg/ml)	Loading Dose (µl)	N	Flux ($\mu g/cm^2/hr$)
1. 50/49/1				
$EtOH/H_2O$/GMO	80	400	3	534.8 ± 56.2
	40	400	3	179.1 ± 51.6
	20	400	3	126.7 ± 52.8
2. 50/49/1				
$EtOH/H_2O$/GMO	80	75	3	96.5 ± 9.2
	40	75	9	37.4 ± 11.0
	20	75	3	25.1 ± 1.9
3. 50/44/5/1				
$EtOH/H_2O$/Gly/GMO	80	75	6	78.4 ± 36.5
	40	75	9	26.7 ± 9.5

The flux data of Tables 3 and 4 indicate that in each instance the drug release profile was Fickian with flux decreasing with decreasing concentration below saturation.

Similar tests were carried out on ointment and solid matrix systems containing pindolol free base as the hydrophilic drug. Again, systems exhibited classic Fickian dependence of flux on drug concentration.

Example 4

Formulations of testosterone at saturation and below saturation were prepared and tested as in Example 1. The carrier used was $EtOH/H_2O$/Gly/GMO/ML in a ratio of 60/30/5/2.5/2.5. The results of these tests are shown in Table 5 below. The formulations containing 50 mg/ml testosterone were saturated, whereas the systems containing 40 mg/ml and below were subsaturated. The

results are expressed in terms of cumulative permeations at 24 hr (i.e., $\mu g/cm^2$) rather than as flux.

Table 5

Skin	Conc. (mg/ml) Cumulative Permeation at 24 hr ($\mu g/cm^2$)						
	50	40	30	20	15	10	5
1	156.04	189.44	244.37	298.68	-	340.93	-
2	188.24	-	-	407.57	-	564.62	335.57
3	121.68	-	-	317.66	550.48	386.73	-
4	128.25	-	-	429.22	386.89	281.79	-
5	130.98	-	-	232.71	212.18	262.63	-
Mean	145.04	189.44	244.37	337.17	383.18	367.34	335.57
SD	24.55	-	-	72.39	138.14	107.96	-

As shown, the permeation was significantly greater when the testosterone was present at subsaturation concentrations. Similar tests were carried out using the following carrier compositions:

$EtOH/H_2O$/Gly/GMO/ML/OA - 60/27.5/5/2.5/2.5/2.5
$EtOH/H_2O$/Gly/GMO/ML - 60/33/5/1/1
$EtOH/H_2O$/Gly/GMO/ML - 60/25/5/5/5
$EtOH/H_2O$/Gly/GMO/ML - 50/35/5/5/5
$EtOH/H_2O$/Gly/GMO/ML/OA - 50/37.5/5/2.5/2.5/2.5

In each instance the formulations below saturation exhibited higher permeations than the corresponding formulation at saturation.

Example 6

Estradiol-containing matrices were prepared by mixing acrylic adhesive (National Starch Durotac 1194), sorbitan monooleate (Arlacel 80) and estradiol at a ratio of 80-X/20/X where X is the proportion (wt%) of estradiol. The cumulative permeation at 24 hr of estradiol from these matrices were tested as above and are reported in Table 7 below. The matrix containing 8% estradiol was saturated; the others were subsaturated.

Table 7

% Estradiol	8%	6%	4%	3%	2%	1%
Cumulative Permeation ($\mu g/cm^2$)	12.93	22.56	44.94	40.88	28.31	11.36
S.D.	5.25	3.03	4.46	6.64	6.24	1.40

As reported in the table, the maximum permeation values observed at subsaturation were approximately three-fold that observed at saturation.

Similar tests were carried out on estradiol-containing matrices in which sorbitan monolaurate was substituted for sorbitan monooleate and in ointments using the carrier EtOH/H_2O/Gly/GMO/ML - 20/60/5/7.5/7.5. In these other estradiol formulations, maximum permeation was observed at estradiol concentrations below saturation.

Example 7

Estradiol-containing matrices were prepared and tested as in Example 6 except that these matrices did not contain permeation enhancer (sorbitan monooleate). The cumulative permeations at 24 hr from these matrices are reported in Table 8 below. The matrix containing 8% estradiol was saturated; the others were subsaturated.

Table 8

% Estradiol	8%	6%	4%	3%	2%	1%
Cumulative Permeation ($\mu g/cm^2$)	9.20	18.42	16.11	21.21	16.55	9.33
S.D.	3.93	0.27	0.64	2.16	1.42	1.84

Example 8

Norethindrone acetate-containing matrices were prepared by mixing a cross-linked acrylic adhesive (Monsanto, Gelva 737), permeation enhancer (a 50:50 (w/w) mix of GMO and ML), and norethindrone acetate at a ratio of 80-X/15/X where X is the proportion of norethindrone acetate. Fluxes from these matrices were tested as above and are reported in Table 9 below. The matrix containing 30% norethindrone acetate was saturated; all others were subsaturated.

Table 9

	% Norethindrone Acetate				
	5%	8%	10%	15%	30%
Flux ($\mu g/cm^2/hr$)	0.44	0.65	0.93	0.46	0.35

As reported, the fluxes from the subsaturated matrices were significantly higher than the flux from the matrix that contained the drug at saturation.

Example 9

Five-layer laminated composites of the general structure described in U.S. Patent No. 4,849,224 were prepared. The layers of the composite (basal to top) were as follows:

1. 5 mil thick silicon-coated polyethylene terephthalate (Tekkote) release liner
2. 1.5 mil thick pressure-sensitive adhesive (AR MA31 acrylic, Adhesives Research)

3. 4 mil thick peel seal disc of ethylene/vinyl acetate copolymer film (Bertek 2216)

4. 2 mil thick microporous polyethylene film (Cotran, 3M) and a 4-5 mil thick cavity (5 cm^2 surface area) filled with an ointment composed of 6.06 mg micronized testosterone, 296.88 mg ethanol, 200.10 mg water, 38.31 mg glycerin, 5.64 mg GMO, 5.27 mg ML, 0.61 mg Vitamin E, and 12.13 mg Klucel.

5. 2 mil thick polyester/ethylene-vinyl acetate laminate (3M Scotchpak 1012) film backing

The release liner and peel seal disc are removed for application to skin. The basal surface area of the reservoir was 5 cm^2.

Placebo composites (four each) and the above composites (four each) were placed on the lower back skin of three hypogonadal men according to the regimen shown in Figure 1. Periodic blood samples were taken and analyzed for testosterone and DHT levels using an established radioimmunoassay.

Figures 1 and 2 show, respectively, the testosterone and DHT levels resulting from these tests.

Figure 3 shows a comparison of the testosterone and DHT blood levels provided by the composite of this example and by the ALZA transscrotal system as reported by Findlay, supra. As shown, the blood levels of testosterone provided by the composite of this example are significantly higher than those provided by the transscrotal system. Correspondingly, the blood levels of DHT are significantly lower for the composite of this example as compared to the transscrotal system.

Figure 4 shows a comparison of the DHT to testosterone ratios provided by the composite of this example and the transscrotal system (again, as reported by Findlay). As shown, the ratio for the composite of this example is significantly less than the ratio for the transscrotal system.

Example 10

A laminated composite of the same structure as that of Example 9 was prepared except that the ointment composition was: 12.4 mg testosterone, 342.40 mg ethanol, 123.40 mg water, 311.90 mg glycerin, 19.2 mg GMO, 19.9 mg ML, 27.7 mg Carbomer 1342 and 10.2 mg 2 N NaOH. The reservoir cavity surface was 7.5 cm^2.

These composites (2 each) were placed on the lower backs of six hypogonadal men for 24 hr. Blood was sampled periodically over that period and their testosterone and DHT levels determined as in Example 9. Figures 5 and 6 report the results of these tests.

Figures 7, 8 and 9 depict average 24 hr plasma levels for testosterone, DHT, and E2 in five hypogonadal subjects following 28 days of continuous transdermal dosing as described above. Open circles in Figures 7 and 8 depict average testosterone and DHT levels determined in 12 normal male volunteers. These data demonstrate that physiological levels and circadian rhythms of testosterone and its active metabolites can be achieved and maintained using nonscrotal transdermal delivery systems according to the present invention.

CLAIMS

1. A device for administering by diffusion a hydrophobic drug transdermally to a patient for a prolonged time period comprising:

(a) a reservoir comprising the drug dissolved in a carrier, the amount and solubility of the drug in the carrier defining a condition of subsaturation that is sufficient to provide a drug skin flux substantially throughout said time period that is significantly greater than the drug skin flux provided when the carrier is saturated with drug; and

(b) means for maintaining the reservoir in diffusional communication with the skin of the patient.

2. The device of claim 1 wherein the reservoir also contains a permeation enhancer.

3. The device of claim 1 or 2 wherein the hydrophobic drug is estradiol, progesterone, norethindrone acetate, or medroxyprogesterone acetate.

4. The device of claim 1, 2 or 3 wherein the prolonged time period is at least about one day.

5. The device of claim 1, 2, 3 or 4 wherein the solubility of the drug in the carrier is in the range of 1 to 500 mg/ml.

7. The device of claim 1, 2, 3, 4 or 5 wherein the drug skin flux substantially throughout the time period is at least about 25% greater than the drug skin flux provided when the carrier is saturated with drug.

8. The device of claim 1, 2, 3, 4, 5, 6 or 7 wherein the concentration of drug in the carrier is about 20% to about 80% the saturation concentration of drug in the carrier substantially throughout the time period.

9. The device of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein said means is the carrier and the carrier is an adhesive.

10. The device of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein said means is a basal adhesive layer underlying the reservoir, an adhesive overlay, or a ring of adhesive that is peripheral to the reservoir and is interconnected to the reservoir.

11. The device of claim 2 wherein the drug is testosterone, the skin is nonscrotal skin, and the drug skin flux substantially throughout the time period is about 5 to 30 $\mu g/cm^2/hr$.

12. The device of claim 11 wherein the carrier is a fluid.

13. The device of claim 12 wherein the carrier is ethanol.

14. The device of claim 13 wherein the permeation enhancer comprises glycerol monooleate and methyl laurate in combination with the ethanol.

15. The device of claim 11 wherein the amount of testosterone in the reservoir is 5 to 50 mg.

16. The device of claim 14 wherein the reservoir contains 5% to 50% by volume glycerin.

17. In a method of administering by diffusion a hydrophobic drug transdermally to a patient for a prolonged time period by placing a reservoir comprising the drug dissolved in a carrier in communication with the skin of the patient the improvement comprising having the concentration of drug in the carrier at below saturation at the start of the period and maintaining subsaturation thereafter for a time sufficient to provide said increase substantially throughout the time period.

18. A method of increasing the flux of a hydrophobic drug from a reservoir of the drug dissolved in a carrier that is in drug delivery communication with an area of unbroken skin of a patient for a prolonged time period above the flux provided when the concentration of drug in the carrier is at saturation comprising having the concentration of drug in the carrier at below saturation at the start of the period and maintaining subsaturation thereafter for a time sufficient to provide said increase substantially throughout the time period.

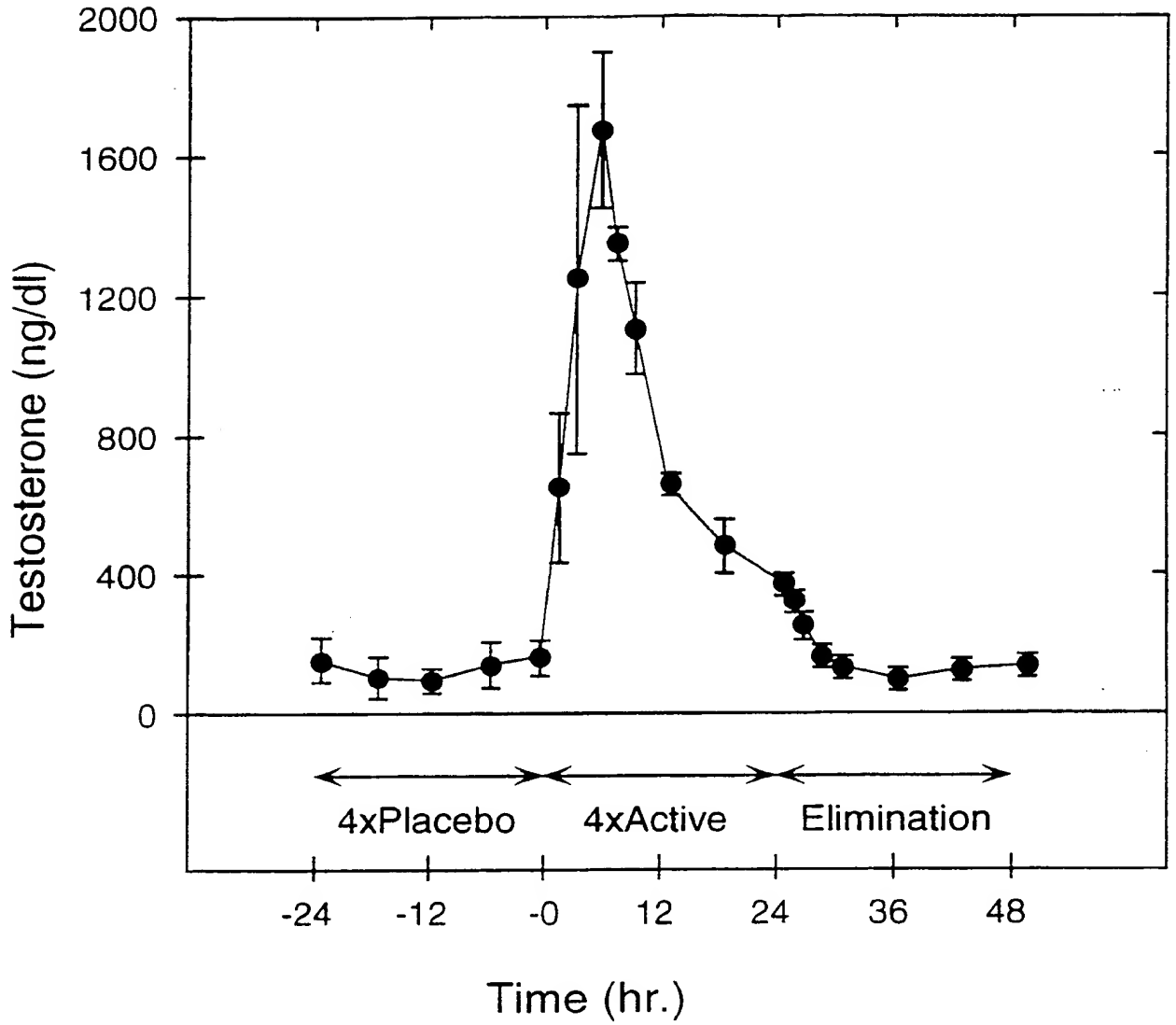

Figure 1

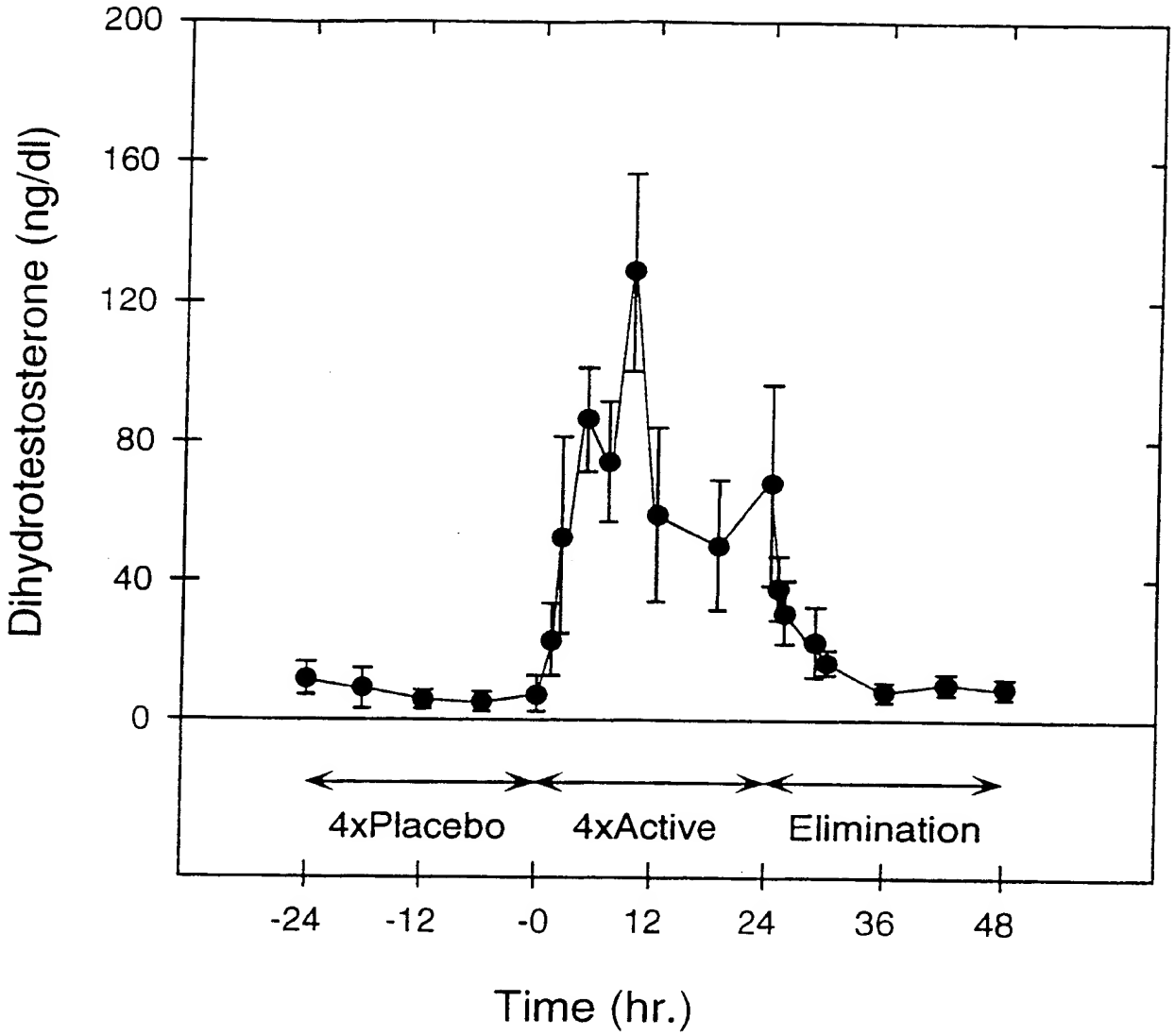

Figure 2

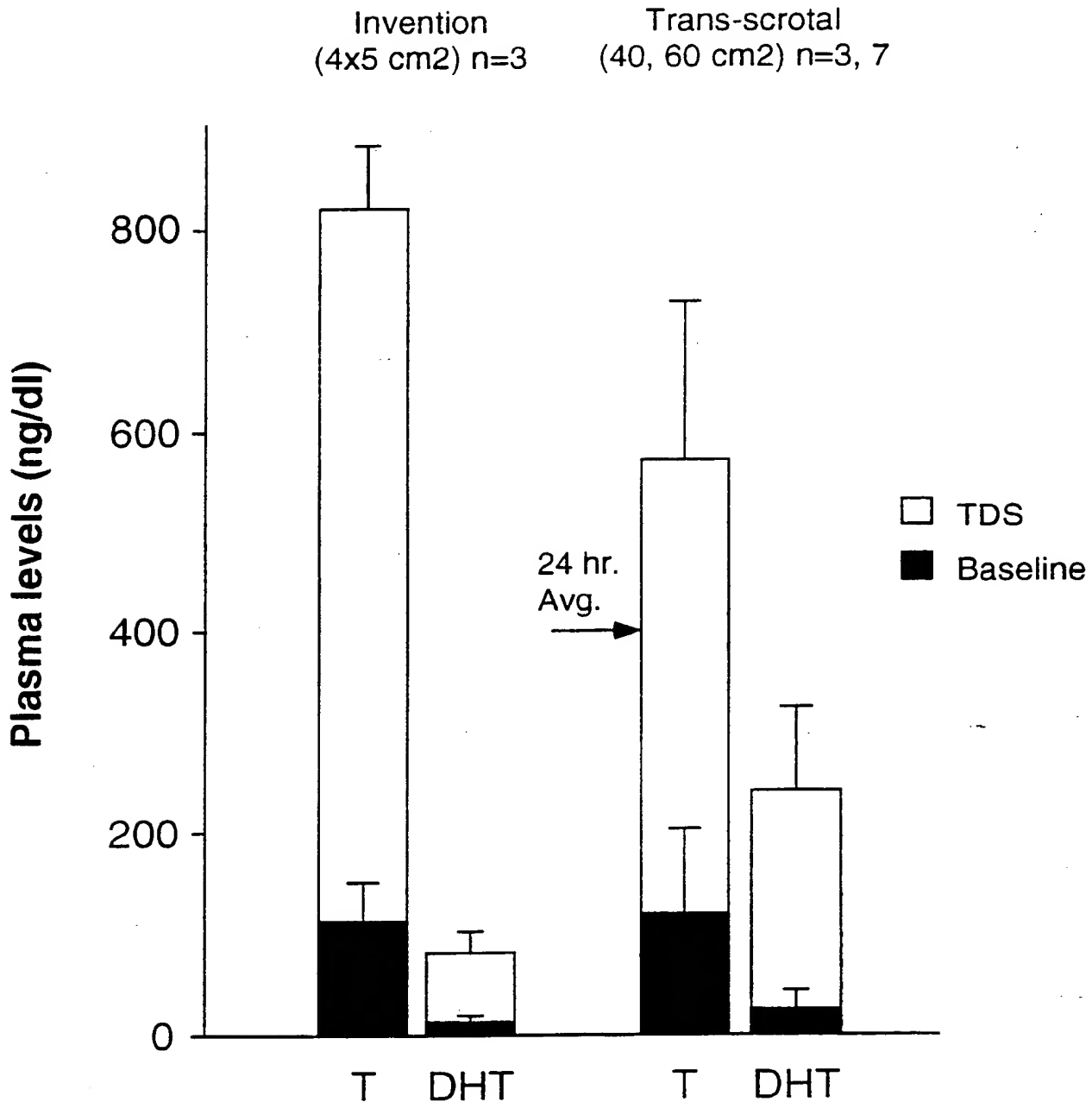

Figure 3

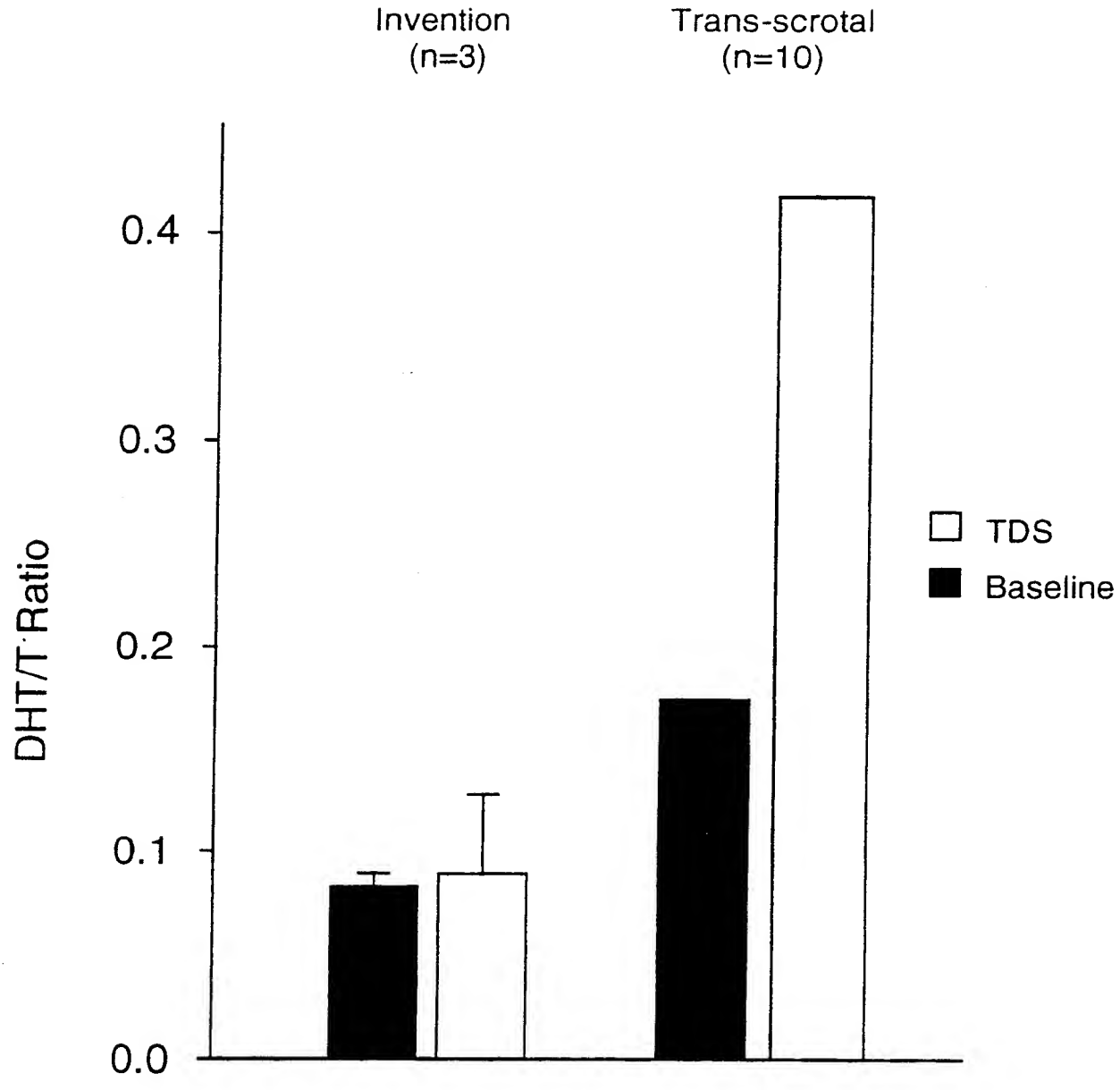

Figure 4

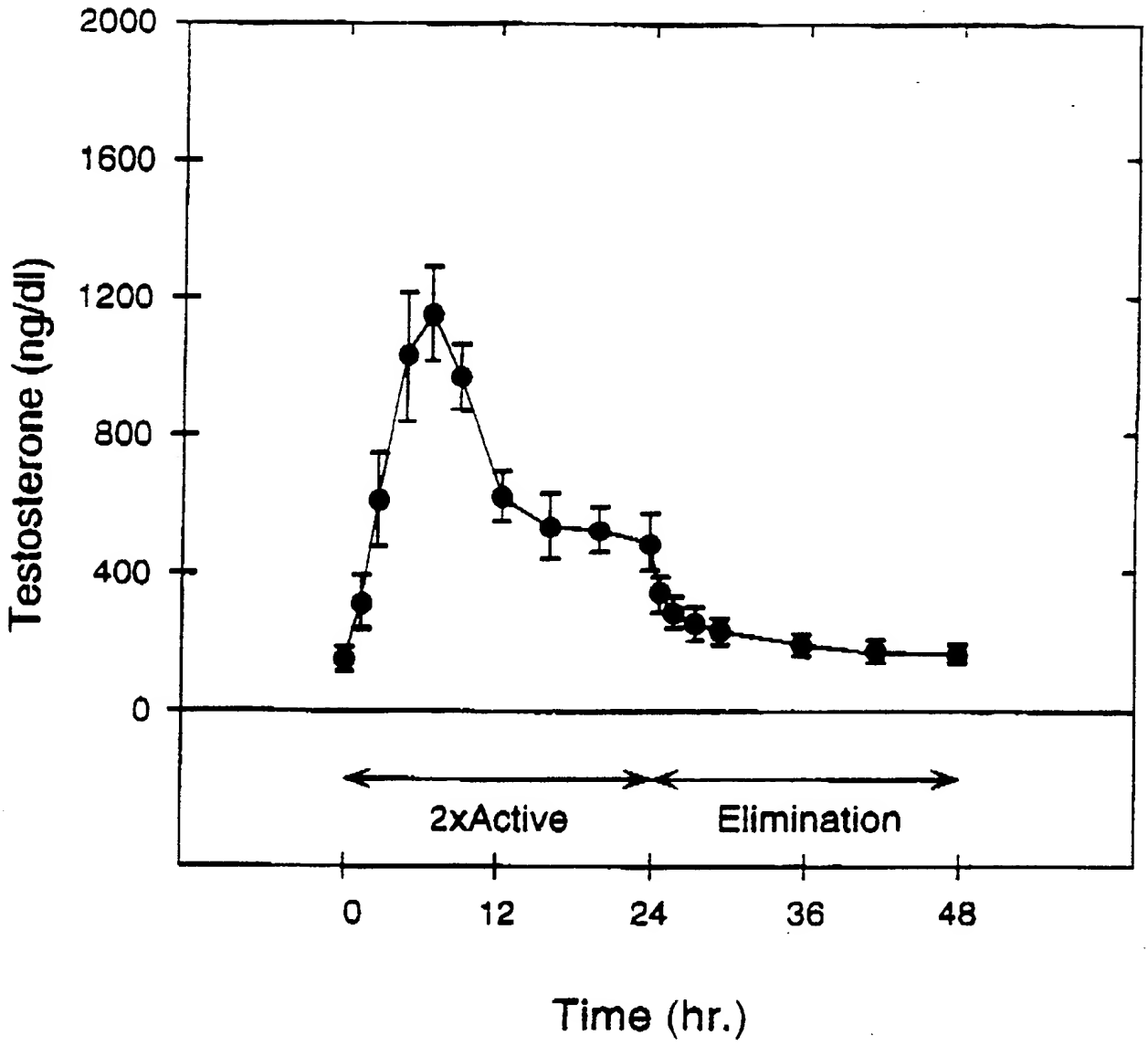

Figure 5

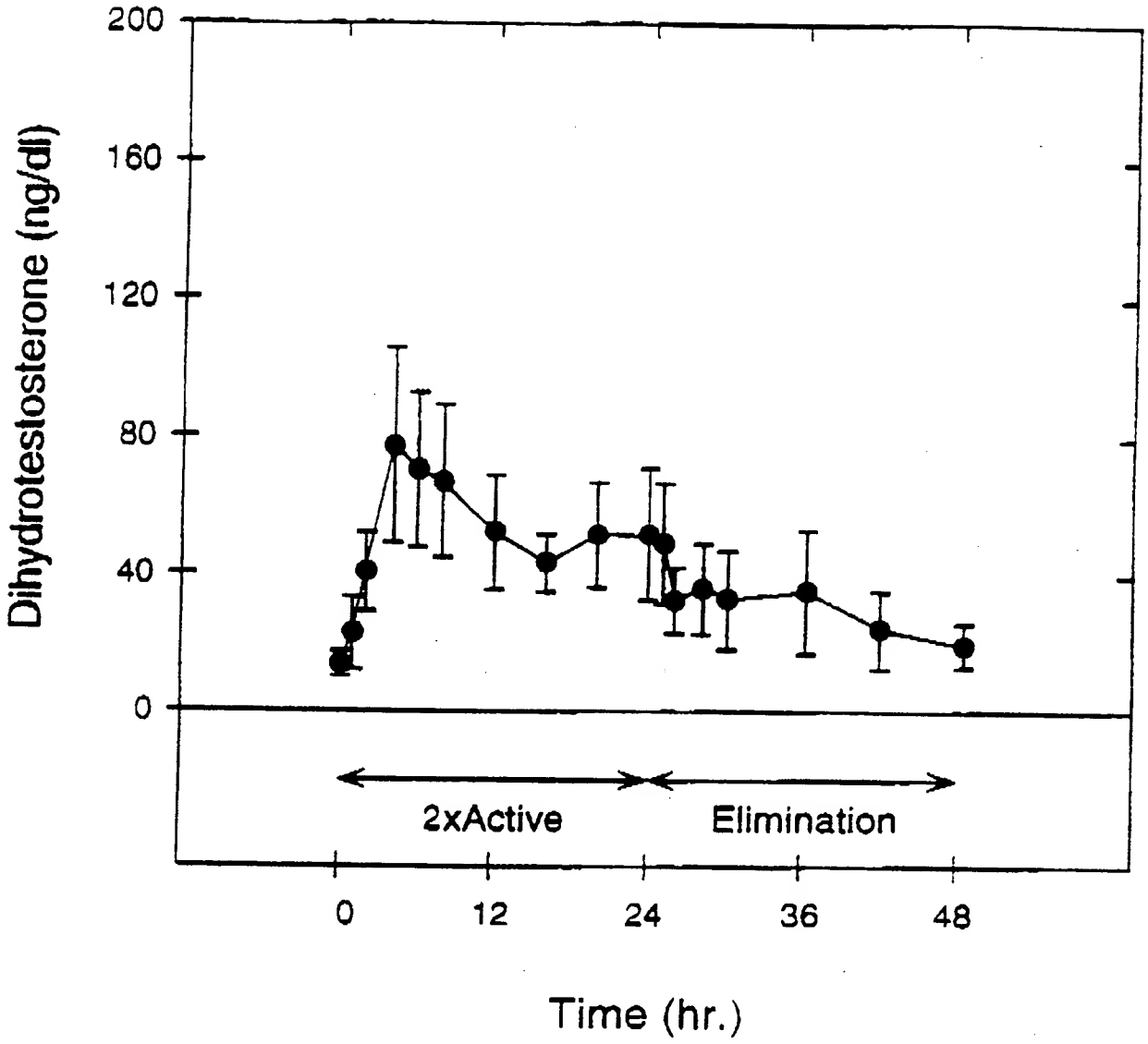

Figure 6

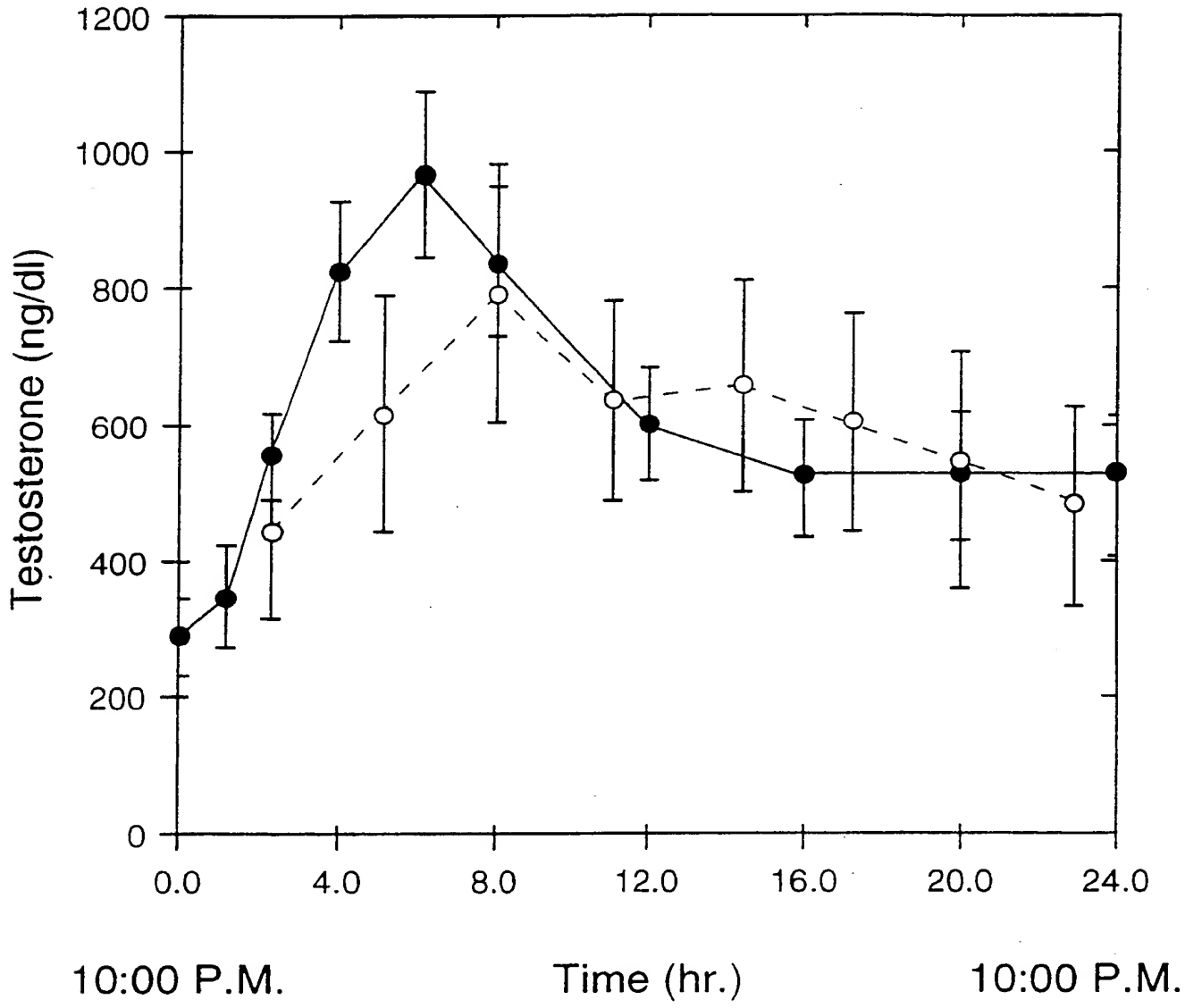

Figure 7

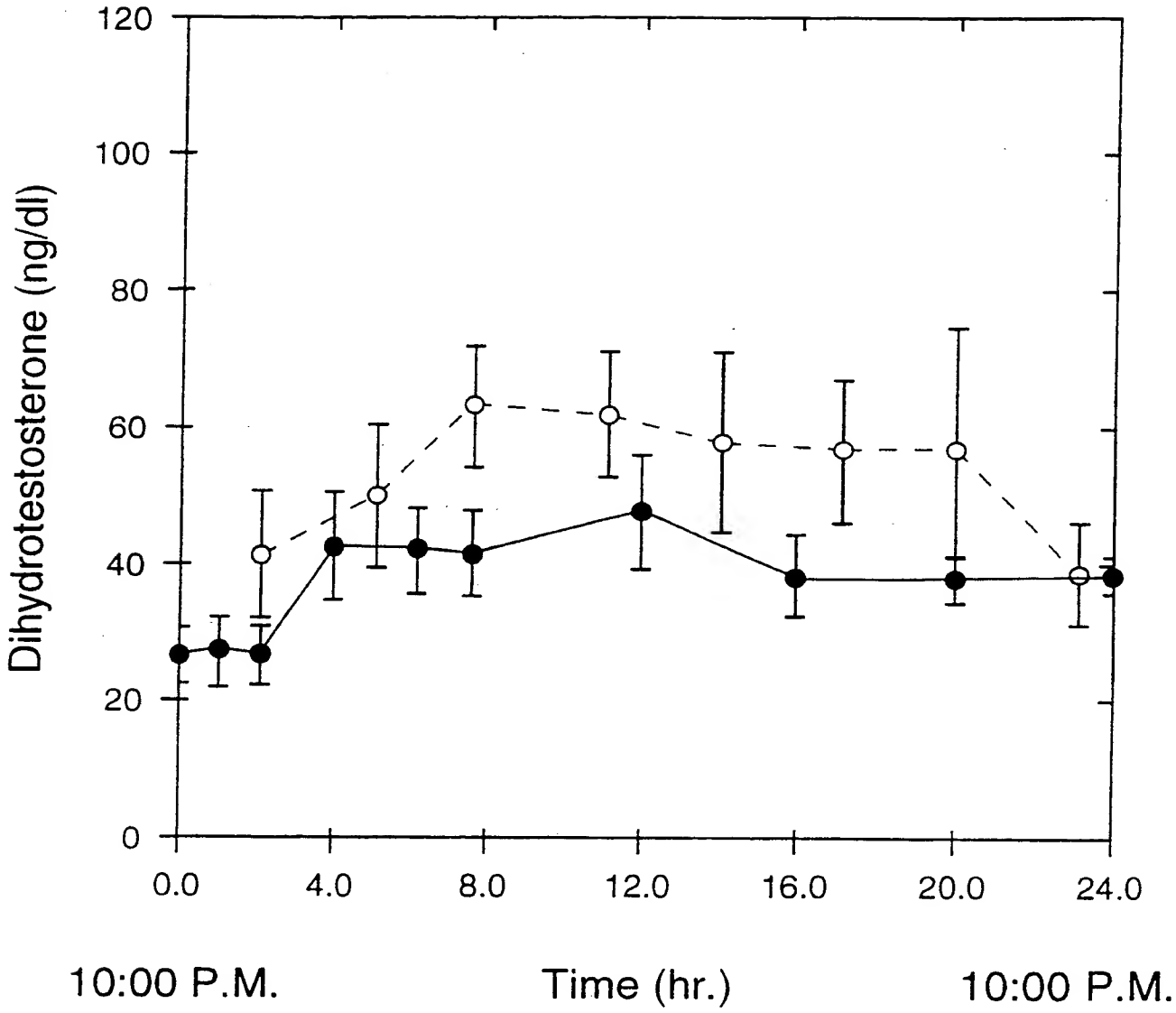

Figure 8

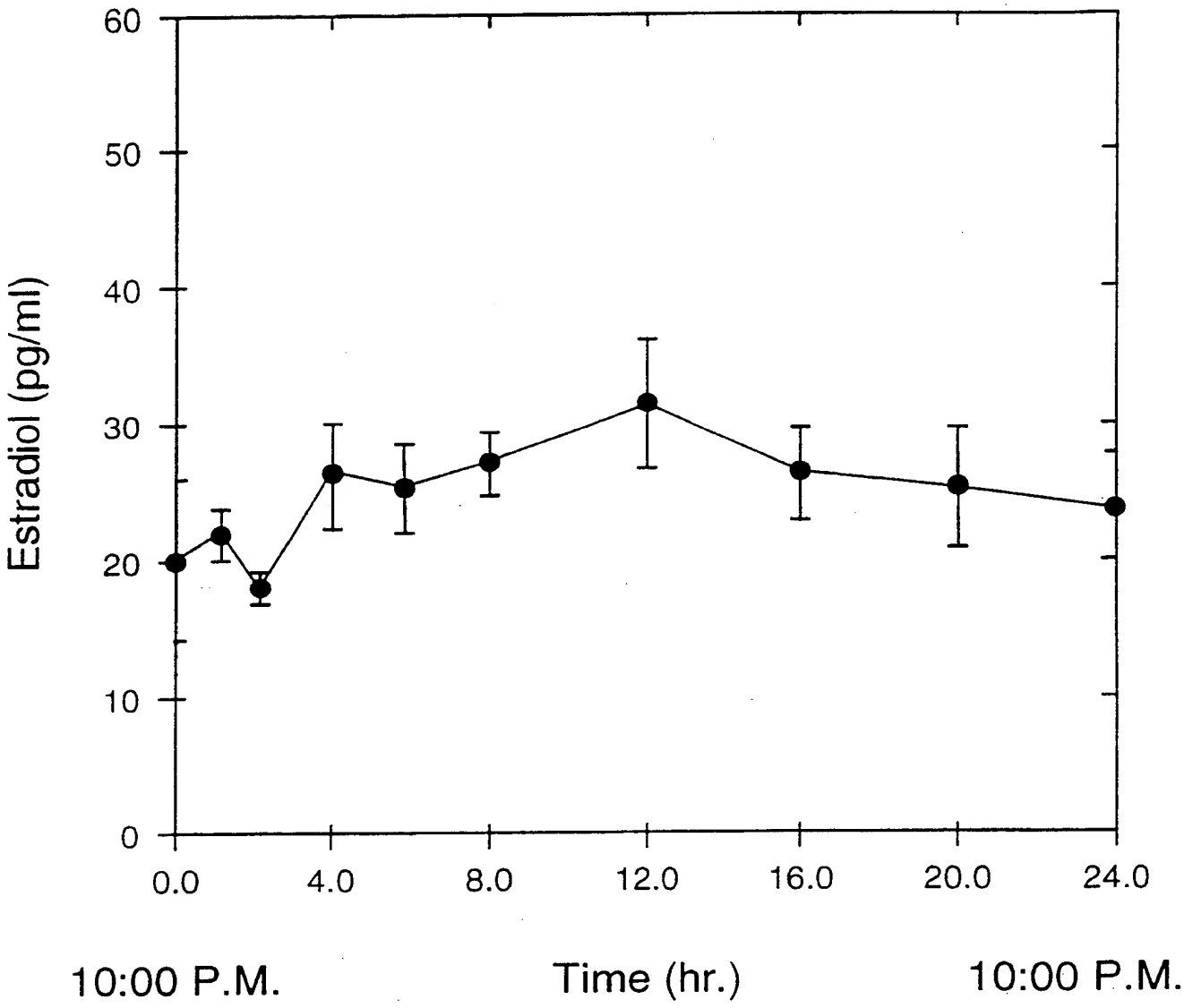

Figure 9

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09408

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61M 37/00

U.S. CL. 424/448

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/448, 449; 514/946, 947

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X / Y	US, A, 4,820,720 (SANDERS ET AL) 11 APRIL 1989 See entire document.	1-3 / 11-18
X / Y	US, A, 4,855,294 (PATEL ET AL) 08 AUGUST 1989 See entire document.	1-3 / 11-18
X / Y	US, A, 4,906,463 (CLEARY ET AL) 06 MARCH 1990 See entire document.	1-3 / 11-18
Y, P	US, A, 5,059,426 (CHIANG ET AL) 22 OCTOBER 1991 See entire document.	1-3, 11-18

* Special categories of cited documents: [10]

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09 MARCH 1992	18 APR 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Thurman K. Page

Form PCT/ISA/210 (second sheet) (Rev.11-87)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [X] Claim numbers 4,5,7–10, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

CORRECTED VERSION *

PCT

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Published
With international search report.

(54) Title: SUBSATURATED TRANSDERMAL DRUG DELIVERY DEVICE EXHIBITING ENHANCED DRUG FLUX

(57) Abstract

Transdermal administration of hydrophobic drugs via a diffusion mechanism in which the drug is dissolved in a carrier at concentrations that are 10 % to 80 % of the saturation concentration. The flux of drug from the device is non-Fickian and is substantially greater than the flux observed when the drug is at saturation.

* (Referred to in PCT Gazette No. 19/1992, Section II)

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+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

SUBSATURATED TRANSDERMAL DRUG DELIVERY DEVICE EXHIBITING ENHANCED DRUG FLUX

Description

Technical Field

This invention is in the field of transdermal drug administration. More particularly it relates to a device and method that provides the drug at unexpectedly high flux.

Background

Transdermal drug delivery devices typically comprise a drug reservoir composed of the drug and a carrier from which the drug is released by diffusion. Examples of such devices are described in "Transdermal Drug Delivery Systems," U.S. Pharmacist, pp. 49-78.

Fick's Law has classically been used to characterize the drug release kinetics of such diffusional devices. According to this law the maximum flux of drug from such a device occurs when the concentration of drug in the carrier is at saturation. Correlatively, the art teaches that the maximum flux of the drug across skin (when the skin is not a rate controlling barrier to the drug) from a given drug-carrier combination also occurs when the concentration of drug in the carrier is at saturation. Since maximum skin flux is desired with most drugs, diffusional devices have traditionally been designed to maintain saturation conditions in the carrier over the dispensing lifetime of the device.

Applicants have now unexpectedly discovered that the maximum skin flux from diffusional devices in which the drug is hydrophobic occurs when the drug is maintained below saturation in the carrier. This finding is totally contrary to the conventional wisdom followed in the transdermal drug device art. Further, applicants have employed this discovery to permit testosterone to be delivered across nonscrotal skin at therapeutically effective levels. As discussed in detail below, the art teaches that effective transdermal delivery of testosterone can only be achieved through scrotal skin.

Some prior patents have suggested in passing that while it is desirable to maintain the concentration of drug at saturation because maximum flux occurs there at, that the drug concentration could be below saturation. See for instance U.S. Pats. Nos. 4,568,343; 4,645,502; 4,816,258; 4,863,738; 4,865,848; and 4,908,027. These patents, however, fail to suggest maintenance of subsaturation levels of drug throughout the dispensing lifetime or that any increase in skin flux could be achieved with hydrophobic drugs under such conditions.

Testosterone therapy is currently indicated for treatment of male hypogonadism, anemia, breast cancer, and hereditary angioedema. It is also being considered for treating a variety of other conditions such as male osteoporosis that appear to be mediated by androgen deficiency. Traditional modalities for administering testosterone have included: intramuscular injection of long-acting testosterone esters such as the enanthate because testosterone itself is rapidly degraded by the liver if administered orally; oral administration of testosterone undecanoate, which provides systemically available testosterone; and subcutaneous implantation of

fused testosterone pellets. None of these traditional modalities provides totally physiological levels or circadian patterns of testosterone and its active metabolites, dihydrotestosterone (DHT) and estradiol (E_2).

It is known that steroids, including testosterone, are absorbed through skin. However, the permeability to testosterone of skin areas that are normally used for transdermal delivery (e.g., the neck, back, chest, arms) is too low to permit delivery of the amounts of testosterone needed for therapy (typically 5-10 mg/day) through a limited area of skin. In this regard, Korennan, S.G., et al., (Am J Med (1987) 83:471-478) in an article on testosterone delivery for treating hypogonadism concluded "a more permeable skin area with a much higher absorption rate was required to provide programmed transdermal delivery to a limited area." This led Korennan et al. to select scrotal skin--which is highly permeable to testosterone--as a site for testosterone delivery. The article further describes a transscrotal delivery system developed by ALZA Corporation. U.S. 4,704,282 describes that system in detail. It consists of a polymer matrix that contains testosterone at subsaturation levels and a fabric reinforcement incorporated into the matrix that also is a limited solvent for testosterone. The patent indicates that a subsaturated matrix is used because a declining testosterone release rate is desired. The reinforcing fabric, in addition to providing a structural support function, is said to act as a secondary reservoir for testosterone which has the effect of flattening the release rate profile (see Figure 2 of the patent). While the patent states that permeation enhancers may be present in the matrix, no examples of the use of such enhancers are described. The patent gives no data on the

skin flux of testosterone provided by its systems. Example 2 of the patent states that its system may be applied to nonscrotal skin, particularly the thigh, to produce "similar results" as when applied to scrotal skin. This statement is, however, contradicted by the later Korennan et al. article (which also originates from ALZA Corporation) which reports that systems applied to the thigh did not give increased blood levels of testosterone.

Ahmed, S.R., et al. (J Clin Endocrinol Metab (1988) 66:546-557) and Findlay, J.C. (J Clin Endocrinol Metab (1989) 68:369-373) report that the 60 cm^2 ALZA transscrotal system delivers about 3.7 mg/day and produces low-normal testosterone levels in hypogonadal men. Such dosages are believed to be somewhat less than the amount needed to mimic endogenous production (5-10 mg/day). Furthermore, since scrotal skin has a relatively high level of 5α-reductase, continuous transscrotal delivery of testosterone produces levels of DHT and DHT/testosterone ratios 4- to 5-fold greater than normal. Such abnormal levels and ratios may give rise to undesirable side effects.

In sum, the art teaches away from transdermally administering testosterone through nonscrotal skin because of the low permeability of such skin to testosterone. Transscrotal delivery of testosterone is taught, but such delivery is associated with high DHT and DHT/testosterone ratio levels and does not provide a level of testosterone delivery that mimics endogenous production. Further, scrotal skin is sensitive and limited in area, which may result in discomfort and poor patient acceptance of this modality of delivery.

Disclosure of the Invention

As described above, the invention is based on the discovery that in the case of transdermal administration of hydrophobic drugs from a diffusional device, maximum skin flux is achieved at concentrations of drug in the carrier that are below saturation. In some instances the increase in flux at subsaturation is dramatically higher than at saturation. The invention thus takes the form of devices for and methods of administering hydrophobic drugs transdermally that are based on this finding.

Accordingly, in one aspect, the invention is a device for administering by diffusion a hydrophobic drug transdermally to a patient for a prolonged time period comprising:

(a) a reservoir comprising the drug dissolved in a carrier, the amount and solubility of the drug in the carrier defining a condition of subsaturation that is sufficient to provide a drug skin flux substantially throughout said time period that is significantly greater than the drug skin flux provided when the carrier is saturated with drug; and

(b) means for maintaining the reservoir in drug delivery communication with the skin of the patient.

In another aspect the invention is an improvement in the method for administering a hydrophobic drug transdermally to a patient for a prolonged time period by placing a reservoir comprising the drug dissolved in a carrier in communication with the skin of the patient which improvement comprises having the concentration of the drug in the carrier below saturation at the start of the period and maintaining subsaturation thereafter for a sufficient time to provide substantially throughout the time period a drug skin flux that is

substantially greater than the drug skin flux provided when the carrier is saturated with the drug.

Another aspect of the invention is a method of increasing the flux of a hydrophobic drug from a reservoir of the drug dissolved in a carrier that is in drug delivery communication with an area of unbroken skin of a patient for a prolonged time period above the flux provided when the concentration of drug in the carrier is at saturation comprising having the concentration of drug in the carrier at below saturation at the start of the period and maintaining subsaturation thereafter for a time sufficient to provide said increase substantially throughout the time period.

Still another aspect of the invention is a device for administering testosterone transdermally across an area of unbroken nonscrotal skin at a flux from 5 to 30 $\mu g/cm^2/hr$ comprising:

(a) a reservoir comprising testosterone dissolved in a carrier, and a skin permeation enhancer, the amount and solubility of testosterone in the carrier defining a condition of subsaturation that causes enhanced permeation of testosterone through nonscrotal skin and wherein the combined permeation enhancement resulting from said condition of subsaturation and said permeation enhancer provide said flux; and

(b) means for maintaining the reservoir in diffusional communication with said area of unbroken nonscrotal skin.

Brief Description of the Drawings

Figures 1 and 2 are graphs of the results of the tests described in Example 9.

Figures 3 and 4 are bar graphs comparing the results of the tests described in Example 9 with the prior art.

Figures 5 and 6 are graphs of the test results of Example 10.

Figures 7, 8 and 9 are graphs of data described in Example 10.

Modes for Carrying Out the Invention

The term "drug" as used to describe the principal active ingredient of the invention device intends a biologically active compound or mixture of compounds that has a therapeutic, prophylactic and/or physiological effect on the wearer of the device. Examples of the types of drugs that may be used in the device are antiinflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, antidepressants, antipsychotic drugs, tranquilizers, antianxiety drugs, narcotic antagonists, antiparkinsonism agents, cholinergic agonists, anticancer drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistamines, antimigrane agents, vasodilators, hormonal agents, contraceptive agents, diuretics, antihypertensive agents, cardiovascular drugs, and the like.

As used herein the term "hydrophobic" intends that the solubility of the drug in water at room temperature is <50 μg/ml. Specific examples of hydrophobic drugs are steroids such as estrogens, progestogens, testosterone, norgestrel, norethindrone acetate and medroxyprogesterone acetate.

The phrase "prolonged time period" means a period of at least about one day, usually 1-14 days, more

usually 1-7 days. The term "substantially throughout" intends at least about 60% of the time period, more usually at least 80%, and preferably 100% of the period.

The term "skin flux" intends the rate of transfer of drug across skin as measured by the method of Merritt and Cooper (J Controlled Release (1984) 1:161). The units of flux are preferably $\mu g/cm^2/hr$.

The term "significantly greater" that is used to characterize the increase in skin flux achieved through use of the invention will typically denote an increase in skin flux of at least about 25%, usually 25% to 400%, and more usually 50% to 200% over the skin flux provided when the carrier is saturated with the drug.

The term "nonscrotal skin" means human skin excepting the skin of the male human genitalia. It will normally denote the skin of relatively hair-free portions of the body such as the limbs, back, chest, buttocks, hips, and neck.

As used here, the term "testosterone therapy" intends treatment of any indication for which testosterone is indicated, including, without limitation, primary, secondary and other male hypogonadal states in adults and adolescents, anemia, hereditary angioedema, male contraception, male infertility disorders, post-surgical recovery, male impotence, hormone replacement in elderly males, and hypogonadal states associated with AIDS. Primary (testicular) hypogonadism disorders include Klinefelder's Syndrome, viral orchitis, and low testosterone production caused by trauma, radiation or chemotherapy, or alcohol abuse. Secondary (hypothalamic/pituitary) disorders include those associated with hypothalamic hypogonadism, suprasellar tumors, and pituitary tumors. Other male hypogonadism

disorders include those associated with aging, systemic illnesses, stress, and diabetes mellitus.

The phrase "corresponds substantially to endogenous blood levels produced by healthy young adult male humans" intends a blood level profile that closely approximates the circadian rhythm of testosterone production shown in Figure 7 of the drawings.

The devices of the invention release drug continuously by diffusion. In this mode, the driving force is the difference in drug concentration between the device reservoir and the skin and underlying tissue. The drug, which is entirely dissolved in the carrier or vehicle in the case of the present invention, permeates through the carrier to the skin. The carrier is, of course, in drug delivery (diffusional) communication with the skin--which means that it either contacts the skin directly or contacts material interposed between the carrier and the skin that provides a permeation pathway for the drug and, if present, permeation enhancer, to migrate from the reservoir to the skin. The interposed material may be homogeneous, heterogeneous, or be composed of a multiplicity of distinct layers. In any event the interposed material is permeable to the drug and preferably is not a rate-controlling barrier to diffusion (i.e., it is at least as permeable to the drug, and, if present, permeation enhancer, as the carrier).

As indicated above, the carrier or vehicle is permeable to drug. In this regard the diffusion coefficient of the drug in the carrier will usually be between 1×10^{-6} and 1×10^{-12} cm^2/sec, more usually between 1×10^{-7} and 1×10^{-10} cm^2/sec. The solubility of the drug in the carrier should be such that sufficient drug is contained in the device to provide the required cumulative dose of drug, which will vary from drug to

drug. At the same time, the solubility should not be so low as to require the device to be impractically large in area or thickness. In most instances, the solubility of drug in the carrier will be in the range of 1 to 500 mg/ml, more usually 1 to 200 mg/ml (measured at room temperature). The amount of drug in the carrier will normally range between 0.001 and 100 mg, more usually between 1 and 50 mg. The thickness of the reservoir will usually be about 0.01 to 5 mm, more usually 0.03 to 2 mm. The area of the device in drug delivery (diffusional) contact with the skin will usually be between about 1 and 150 cm^2, more usually between 5 and 40 cm^2.

In the case of testosterone, its solubility in the carrier should be such that sufficient testosterone is contained in the device to provide the required cumulative dose of testosterone, which will normally be in the range of 5 to 10 mg/day. At the same time, the solubility should not be so low as to require the device to be impractically large in area or thickness. The amount of testosterone in the carrier will normally range between 5 and 50 mg per unit dosage form, more usually between 10 and 20 mg. The thickness of the reservoir will usually be about 0.01 to 5 mm, more usually 0.03 to 2 mm.

The carrier may be a solid or semi-solid polymer that enables the device to be a "solid-state" device (i.e., no liquid component at room temperature). Alternatively, the carrier may be in a fluid form (e.g., liquid, gel, emulsion, suspension, and be aqueous or nonaqueous. Examples of fluid carriers that may be used are alcohols such as ethanol, alcohol-water mixtures, and low molecular weight polymers such as polyethylene glycol. Examples of solid polymeric carriers that may be used in this invention are polyacrylates,

polymethacrylates, silicone polymers, polyalkyloxides, natural and synthetic rubbers and the dermatologically acceptable adhesives described in U.S. 3,934,097.

In the case of testosterone, the carrier is preferably a fluid. Examples of fluid carriers that may be used are alcohols such as ethanol, alcohol-water mixtures, and low molecular weight polymers such as polyethylene glycol. Ethanol is preferred and also provides permeation enhancement. In the case of ethanol, the carrier normally constitutes 20% to 70% by volume of the reservoir, more usually 40% to 60%, and preferably approximately 50%. Alternatively, the carrier may be a solid or semisolid matrix suxh as a pressure-sensitive adhesive.

The concentration of drug in the carrier will usually be between 10% and 80% of saturation concentration, usually 15% and 60% of saturation substantially throughout the administration period. Depending upon the nature of the carrier and other components of the reservoir (permeation enhancers), the concentration of drug relative to saturation may decrease or increase over the administration period. If the solubility of the drug in the carrier (whether modified or not by other components) remains constant over the period, the concentration relative to saturation will decrease. On the other hand, if the solubility decreases (for instance, through delivery of a permeation enhancer that also increases solubility), then the concentration relative to saturation will increase.

A permeation enhancer may be administered concurrently with the drug in order to further increase the skin flux of drug across the skin. For testosterone, an enhancer is necessary. The enhancer may also be contained within the reservoir or be administered from a

separate reservoir underlying or overlying the drug reservoir. For design simplicity, when used, the enhancer will preferably be contained in the drug reservoir. Aside from the requirements that the enhancer be compatible with the drug and carrier, there are no limitations on the enhancers that may be used in the invention. Examples of enhancers known in the art are those described in U.S. Pats. Nos. 3,989,816; 4,316,893; 4,863,970; 4,764,379; 4,537,776; and EPA (Pub. No.) 272,987, the disclosures of which, as they relate to enhancers, are incorporated herein by reference. A preferred enhancer for use with testosterone is a mixture of ethanol (also carrier), glycerol monooleate (GMO) and methyl laurate (ML). The amounts of each of GMO and ML in the reservoir will normally be 0.5% to 5% by volume, preferably approximately 2.5%. The amount of ethanol will be that previously described. The reservoir may also contain amounts of other materials such as gelling agents and antiirritants. Glycerin is a preferred antiirritant and may be present at 5% to 50%, preferably 20% to 30% by volume. The use of glycerin as an anti-irritant is described in U.S. 4,855,294.

The skin testosterone flux provided by the invention is about 5 to 30 $\mu g/cm^2/hr$, and preferably about 10 to 20 $\mu g/cm^2/hr$. In contrast, the testosterone skin flux provided by conventional transdermal administration is typically less than 0.5 $\mu g/cm^2/hr$. The high skin fluxes realized through the invention are a result of enhancement due to the subsaturation concentration of testosterone in the carrier and the enhancement due to the permeation enhancer.

For treating male hypogonadism it is desired to provide daily administration in a 24-hr release rate profile that mimics the endogenous diurnal testosterone

production pattern. This in turn leads to a circadian rhythm in testosterone levels. Figure 7 of the drawings (open circles) shows a representative circadian rhythm of testosterone production over a one-day period. As shown, testosterone levels peak in the early morning hours and then decline to trough values in the evening.

The device of the invention may be embodied in various types of structures known in the transdermal drug delivery art. For instance, the drug reservoir, which is the most important component of the device, may comprise a simple matrix of a subsaturated solution of the drug in the carrier or be in the form of a fibrous body impregnated with the subsaturated solution of drug in the carrier. In addition to the reservoir, the device includes means for maintaining the reservoir in drug-delivery communication with the skin. Such means include a carrier which is also an adhesive, a separate basal adhesive layer underlying the reservoir, a peripheral ring of adhesive that is interconnected to the reservoir, an adhesive overlay for the reservoir, and straps. Preferably the means is either an adhesive carrier or a separate underlying adhesive layer. Preferably the device is in the form of a laminated composite.

In addition to the reservoir and affixation means, the device may further include a backing that overlies the reservoir and protects the reservoir and/or prevents back-diffusion of drug from the reservoir, one or more structural layers to provide the device with appropriate mechanical properties, and/or a release liner layer that underlies the reservoir and which is removed prior to use.

These devices may be manufactured by conventional techniques used in the transdermal drug delivery device art. For instance the drug and carrier

may be mixed in the desired proportions to form a homogeneous mix and cast or otherwise applied to a backing layer, followed by lamination to a release liner layer. If a separate basal adhesive layer is desired, it may be cast onto the release liner layer prior to such lamination. As indicated above, the solubility of drug in the carrier and the size (thickness of reservoir and area in drug delivery communication with the skin) are chosen to maintain subsaturation in the reservoir over the desired dispensing lifetime of the device and provide the necessary cumulative dose of drug.

The following examples further illustrate the invention and its unique characteristics. These examples are not intended to limit the invention in any manner. In the following examples *in vitro* steady state transdermal flux across human cadaver skin was determined using the method of Merritt and Cooper, supra. Unless otherwise indicated percentages and proportions are by volume.

Example 1

Formulations of progesterone at varying concentrations were made by mixing progesterone with the indicated ingredients and applied to cadaver skin. The transdermal fluxes for these formulations are reported in Table 1 below. The meanings of the abbreviations that appear in the table are: Gly = glycerine; GDO = glycerol dioleate; ML = methyl laurate; OA = oleic acid; GMO = glycerol monooleate.

Table 1

Enhancer Systems*	Progesterone Conc. (mg/ml)	N	Flux ($\mu g/cm^2/hr$)
1. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GDO/ML/OA	75.0	8	2.12 ± 0.47
2. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GDO/ML/OA	50	18	4.51 ± 1.37
3. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GDO/ML/OA	25	3	5.52 ± 1.38
4. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	75	8	3.35 ± 2.18
5. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	50	18	7.63 ± 3.00
6. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	37.5	6	8.18 ± 0.90
7. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	25	18	6.37 ± 1.88
8. 60/22.5/10/2.5/2.5/2.5 EtOH/H_2O/Gly/GMO/ML/OA	10	3	1.84 ± 0.33

* Systems #1 - #8 were gelled by adding 2.5% (w/v) Carbopol 1342, pHs were unadjusted (3.2 - 3.5) and the loading doses were 0.075 ml.

In Table 1, systems 1 and 4 contain progesterone at saturation. Systems 1-3 are alike except for progesterone concentration, and systems 4-8 are alike

except for progesterone concentration. The two sets of systems are alike except that one (1-3) contains GDO and the other (4-8) contains GMO. As shown by the flux data in Table 1, the flux is significantly greater in those systems (except 8) in which the progesterone is at subsaturated concentrations (systems 1, 3, 5-7) than when the progesterone is at saturation.

Example 2

Additional progesterone systems were formulated and tested as in Example 1. The results of these tests are shown in Table 2 below. Abbreviations are as in Example 1. Progesterone was present at saturation in system 1 and below saturation in systems 2-6.

Table 2

Enhancer Systems*	Progesterone Conc. (mg/ml)	N	Flux ($\mu g/cm^2/hr$)
1. 60/22.5/10/2.5/2.5/2.5 $EtOH/H_2O$/Gly/GDO/ML/OA	50	12	6.01 ± 1.73
2. 60/28/10/1/1 $EtOH/H_2O$/Gly/GMO/ML	30	3	13.03 ± 3.35
3. 60/28/10/1/1 $EtOH/H_2O$/Gly/GMO/ML	25	3	12.98 ± 2.06
4. 60/28/10/1/1 $EtOH/H_2O$/Gly/GMO/ML	20	9	15.89 ± 6.81
5. 60/28/10/1/1 $EtOH/H_2O$/Gly/GMO/ML	15	12	13.13 ± 1.87
6. 60/28/10/1/1/1 $EtOH/H_2O$/Gly/GMO/ML	10	5	11.13 ± 1.98

* Systems were gelled by adding 2.5% (w/v) Carbopol 1342 and the loading doses were 0.075 ml.

As in Example 1, the fluxes of progesterone at concentrations below saturation were significantly greater than at saturation.

Example 3

This Example shows that the phenomenon of higher drug flux at subsaturation unexpectedly occurs only with hydrophobic drugs.

Formulations of the hydrophilic drugs oxybutynin HCl and mecamylamine HCl were prepared and tested as in Examples 1 and 2. Tables 3 and 4 below report the results of those tests. The formulations of Table 3 containing oxybutynin HCl at 40 mg/ml were saturated and the formulations of Table 4 containing 80 mg/ml of mecamylamine HCl were saturated. All other systems were at drug concentrations below saturation.

Table 3

Enhancer Systems	Oxybutyrin Conc. (mg/ml)	N	Flux ($\mu g/cm^2/hr$)
1. 40/53/5/2 EtOH/H_2O/Gly/GMO	40	4	29.1 ± 11.2
	20	12	16.9 ± 5.2
	10	6	13.3 ± 2.6
	5	3	5.6 ± 0.9
2. 40/54/5/1 EtOH/H_2O/Gly/GMO	40	5	38.8 ± 18.9
	20	12	17.5 ± 5.1
	10	6	10.1 ± 3.3
	5	3	8.0 ± 1.4
3. 30/63/5/2 EtOH/H_2O/Gly/GMO	40	6	23.9 ± 10.0
	20	12	14.8 ± 6.1
	10	9	8.3 ± 3.8
	5	3	2.2 ± 0.2
4. 30/64/5/1 EtOH/H_2O/Gly/GMO	40	6	27.5 ± 13.1
	20	15	13.6 ± 5.2
	10	6	5.4 ± 2.5
	5	3	1.7 ± 0.3

Table 4

Enhancer Systems	Mecamylamine Conc. (mg/ml)	Loading Dose (µl)	N	Flux ($\mu g/cm^2/hr$)
1. 50/49/1 EtOH/H_2O/GMO	80	400	3	534.8 ± 56.2
	40	400	3	179.1 ± 51.6
	20	400	3	126.7 ± 52.8
2. 50/49/1 EtOH/H_2O/GMO	80	75	3	96.5 ± 9.2
	40	75	9	37.4 ± 11.0
	20	75	3	25.1 ± 1.9
3. 50/44/5/1 EtOH/H_2O/Gly/GMO	80	75	6	78.4 ± 36.5
	40	75	9	26.7 ± 9.5

The flux data of Tables 3 and 4 indicate that in each instance the drug release profile was Fickian with flux decreasing with decreasing concentration below saturation.

Similar tests were carried out on ointment and solid matrix systems containing pindolol free base as the hydrophilic drug. Again, systems exhibited classic Fickian dependence of flux on drug concentration.

Example 4

Formulations of testosterone at saturation and below saturation were prepared and tested as in Example 1. The carrier used was EtOH/H_2O/Gly/GMO/ML in a ratio of 60/30/5/2.5/2.5. The results of these tests are shown in Table 5 below. The formulations containing 50 mg/ml testosterone were saturated, whereas the systems containing 40 mg/ml and below were subsaturated. The

results are expressed in terms of cumulative permeations at 24 hr (i.e., $\mu g/cm^2$) rather than as flux.

Table 5

Skin	Conc. (mg/ml) Cumulative Permeation at 24 hr ($\mu g/cm^2$)						
	50	40	30	20	15	10	5
1	156.04	189.44	244.37	298.68	-	340.93	-
2	188.24	-	-	407.57	-	564.62	335.57
3	121.68	-	-	317.66	550.48	386.73	-
4	128.25	-	-	429.22	386.89	281.79	-
5	130.98	-	-	232.71	212.18	262.63	-
Mean	145.04	189.44	244.37	337.17	383.18	367.34	335.57
SD	24.55	-	-	72.39	138.14	107.96	-

As shown, the permeation was significantly greater when the testosterone was present at subsaturation concentrations. Similar tests were carried out using the following carrier compositions:

$EtOH/H_2O$/Gly/GMO/ML/OA - 60/27.5/5/2.5/2.5/2.5
$EtOH/H_2O$/Gly/GMO/ML - 60/33/5/1/1
$EtOH/H_2O$/Gly/GMO/ML - 60/25/5/5/5
$EtOH/H_2O$/Gly/GMO/ML - 50/35/5/5/5
$EtOH/H_2O$/Gly/GMO/ML/OA - 50/37.5/5/2.5/2.5/2.5

In each instance the formulations below saturation exhibited higher permeations than the corresponding formulation at saturation.

Example 6

Estradiol-containing matrices were prepared by mixing acrylic adhesive (National Starch Durotac 1194), sorbitan monooleate (Arlacel 80) and estradiol at a ratio of 80-X/20/X where X is the proportion (wt%) of estradiol. The cumulative permeation at 24 hr of estradiol from these matrices were tested as above and are reported in Table 7 below. The matrix containing 8% estradiol was saturated; the others were subsaturated.

Table 7

	% Estradiol					
	8%	6%	4%	3%	2%	1%
Cumulative Permeation ($\mu g/cm^2$)	12.93	22.56	44.94	40.88	28.31	11.36
S.D.	5.25	3.03	4.46	6.64	6.24	1.40

As reported in the table, the maximum permeation values observed at subsaturation were approximately three-fold that observed at saturation.

Similar tests were carried out on estradiol-containing matrices in which sorbitan monolaurate was substituted for sorbitan monooleate and in ointments using the carrier EtOH/H_2O/Gly/GMO/ML - 20/60/5/7.5/7.5. In these other estradiol formulations, maximum permeation was observed at estradiol concentrations below saturation.

Example 7

Estradiol-containing matrices were prepared and tested as in Example 6 except that these matrices did not contain permeation enhancer (sorbitan monooleate). The cumulative permeations at 24 hr from these matrices are reported in Table 8 below. The matrix containing 8% estradiol was saturated; the others were subsaturated.

Table 8

Cumulative Permeation ($\mu g/cm^2$)	% Estradiol 8%	6%	4%	3%	2%	1%
	9.20	18.42	16.11	21.21	16.55	9.33
S.D.	3.93	0.27	0.64	2.16	1.42	1.84

Example 8

Norethindrone acetate-containing matrices were prepared by mixing a cross-linked acrylic adhesive (Monsanto, Gelva 737), permeation enhancer (a 50:50 (w/w) mix of GMO and ML), and norethindrone acetate at a ratio of 80-X/15/X where X is the proportion of norethindrone acetate. Fluxes from these matrices were tested as above and are reported in Table 9 below. The matrix containing 30% norethindrone acetate was saturated; all others were subsaturated.

Table 9

	% Norethindrone Acetate				
	5%	8%	10%	15%	30%
Flux ($\mu g/cm^2/hr$)	0.44	0.65	0.93	0.46	0.35

As reported, the fluxes from the subsaturated matrices were significantly higher than the flux from the matrix that contained the drug at saturation.

Example 9

Five-layer laminated composites of the general structure described in U.S. Patent No. 4,849,224 were prepared. The layers of the composite (basal to top) were as follows:

1. 5 mil thick silicon-coated polyethylene terephthalate (Tekkote) release liner
2. 1.5 mil thick pressure-sensitive adhesive (AR MA31 acrylic, Adhesives Research)

3. 4 mil thick peel seal disc of ethylene/vinyl acetate copolymer film (Bertek 2216)

4. 2 mil thick microporous polyethylene film (Cotran, 3M) and a 4-5 mil thick cavity (5 cm^2 surface area) filled with an ointment composed of 6.06 mg micronized testosterone, 296.88 mg ethanol, 200.10 mg water, 38.31 mg glycerin, 5.64 mg GMO, 5.27 mg ML, 0.61 mg Vitamin E, and 12.13 mg Klucel.

5. 2 mil thick polyester/ethylene-vinyl acetate laminate (3M Scotchpak 1012) film backing

The release liner and peel seal disc are removed for application to skin. The basal surface area of the reservoir was 5 cm^2.

Placebo composites (four each) and the above composites (four each) were placed on the lower back skin of three hypogonadal men according to the regimen shown in Figure 1. Periodic blood samples were taken and analyzed for testosterone and DHT levels using an established radioimmunoassay.

Figures 1 and 2 show, respectively, the testosterone and DHT levels resulting from these tests.

Figure 3 shows a comparison of the testosterone and DHT blood levels provided by the composite of this example and by the ALZA transscrotal system as reported by Findlay, supra. As shown, the blood levels of testosterone provided by the composite of this example are significantly higher than those provided by the transscrotal system. Correspondingly, the blood levels of DHT are significantly lower for the composite of this example as compared to the transscrotal system.

Figure 4 shows a comparison of the DHT to testosterone ratios provided by the composite of this example and the transscrotal system (again, as reported by Findlay). As shown, the ratio for the composite of this example is significantly less than the ratio for the transscrotal system.

Example 10

A laminated composite of the same structure as that of Example 9 was prepared except that the ointment composition was: 12.4 mg testosterone, 342.40 mg ethanol, 123.40 mg water, 311.90 mg glycerin, 19.2 mg GMO, 19.9 mg ML, 27.7 mg Carbomer 1342 and 10.2 mg 2 N NaOH. The reservoir cavity surface was 7.5 cm^2.

These composites (2 each) were placed on the lower backs of six hypogonadal men for 24 hr. Blood was sampled periodically over that period and their testosterone and DHT levels determined as in Example 9. Figures 5 and 6 report the results of these tests.

Figures 7, 8 and 9 depict average 24 hr plasma levels for testosterone, DHT, and E2 in five hypogonadal subjects following 28 days of continuous transdermal dosing as described above. Open circles in Figures 7 and 8 depict average testosterone and DHT levels determined in 12 normal male volunteers. These data demonstrate that physiological levels and circadian rhythms of testosterone and its active metabolites can be achieved and maintained using nonscrotal transdermal delivery systems according to the present invention.

CLAIMS

1. A device for administering by diffusion a hydrophobic drug transdermally to a patient for a prolonged time period comprising:

(a) a reservoir comprising the drug dissolved in a carrier, the amount and solubility of the drug in the carrier defining a condition of subsaturation that is sufficient to provide a drug skin flux substantially throughout said time period that is significantly greater than the drug skin flux provided when the carrier is saturated with drug; and

(b) means for maintaining the reservoir in diffusional communication with the skin of the patient.

2. The device of claim 1 wherein the reservoir also contains a permeation enhancer.

3. The device of claim 1 or 2 wherein the hydrophobic drug is estradiol, progesterone, norethindrone acetate, or medroxyprogesterone acetate.

4. The device of claim 1, 2 or 3 wherein the prolonged time period is at least about one day.

5. The device of claim 1, 2, 3 or 4 wherein the solubility of the drug in the carrier is in the range of 1 to 500 mg/ml.

7. The device of claim 1, 2, 3, 4 or 5 wherein the drug skin flux substantially throughout the time period is at least about 25% greater than the drug skin flux provided when the carrier is saturated with drug.

8. The device of claim 1, 2, 3, 4, 5, 6 or 7 wherein the concentration of drug in the carrier is about 20% to about 80% the saturation concentration of drug in the carrier substantially throughout the time period.

9. The device of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein said means is the carrier and the carrier is an adhesive.

10. The device of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein said means is a basal adhesive layer underlying the reservoir, an adhesive overlay, or a ring of adhesive that is peripheral to the reservoir and is interconnected to the reservoir.

11. The device of claim 2 wherein the drug is testosterone, the skin is nonscrotal skin, and the drug skin flux substantially throughout the time period is about 5 to 30 $\mu g/cm^2/hr$.

12. The device of claim 11 wherein the carrier is a fluid.

13. The device of claim 12 wherein the carrier is ethanol.

14. The device of claim 13 wherein the permeation enhancer comprises glycerol monooleate and methyl laurate in combination with the ethanol.

15. The device of claim 11 wherein the amount of testosterone in the reservoir is 5 to 50 mg.

16. The device of claim 14 wherein the reservoir contains 5% to 50% by volume glycerin.

17. In a method of administering by diffusion a hydrophobic drug transdermally to a patient for a prolonged time period by placing a reservoir comprising the drug dissolved in a carrier in communication with the skin of the patient the improvement comprising having the concentration of drug in the carrier at below saturation at the start of the period and maintaining subsaturation thereafter for a time sufficient to provide said increase substantially throughout the time period.

18. A method of increasing the flux of a hydrophobic drug from a reservoir of the drug dissolved in a carrier that is in drug delivery communication with an area of unbroken skin of a patient for a prolonged time period above the flux provided when the concentration of drug in the carrier is at saturation comprising having the concentration of drug in the carrier at below saturation at the start of the period and maintaining subsaturation thereafter for a time sufficient to provide said increase substantially throughout the time period.

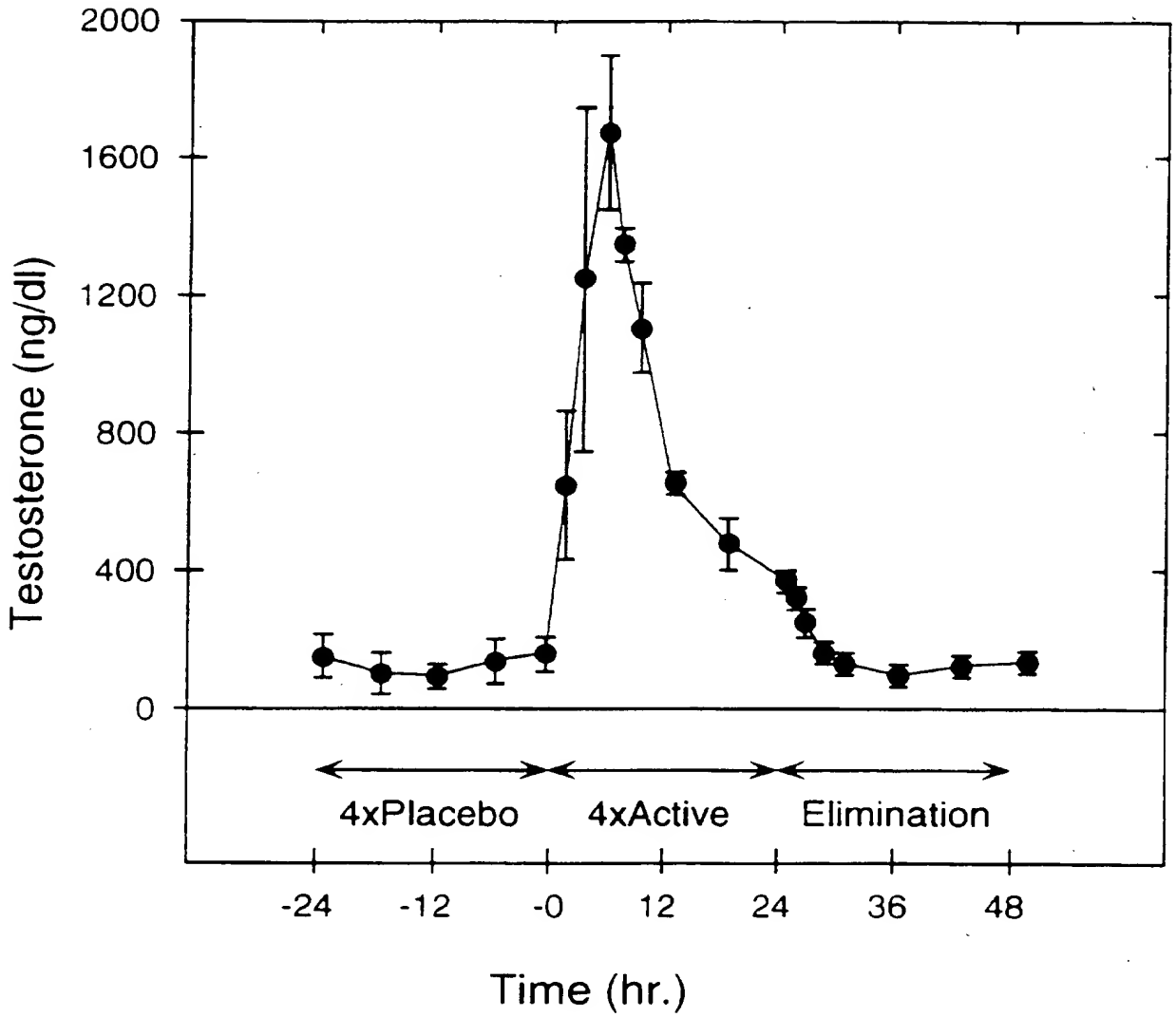

Figure 1

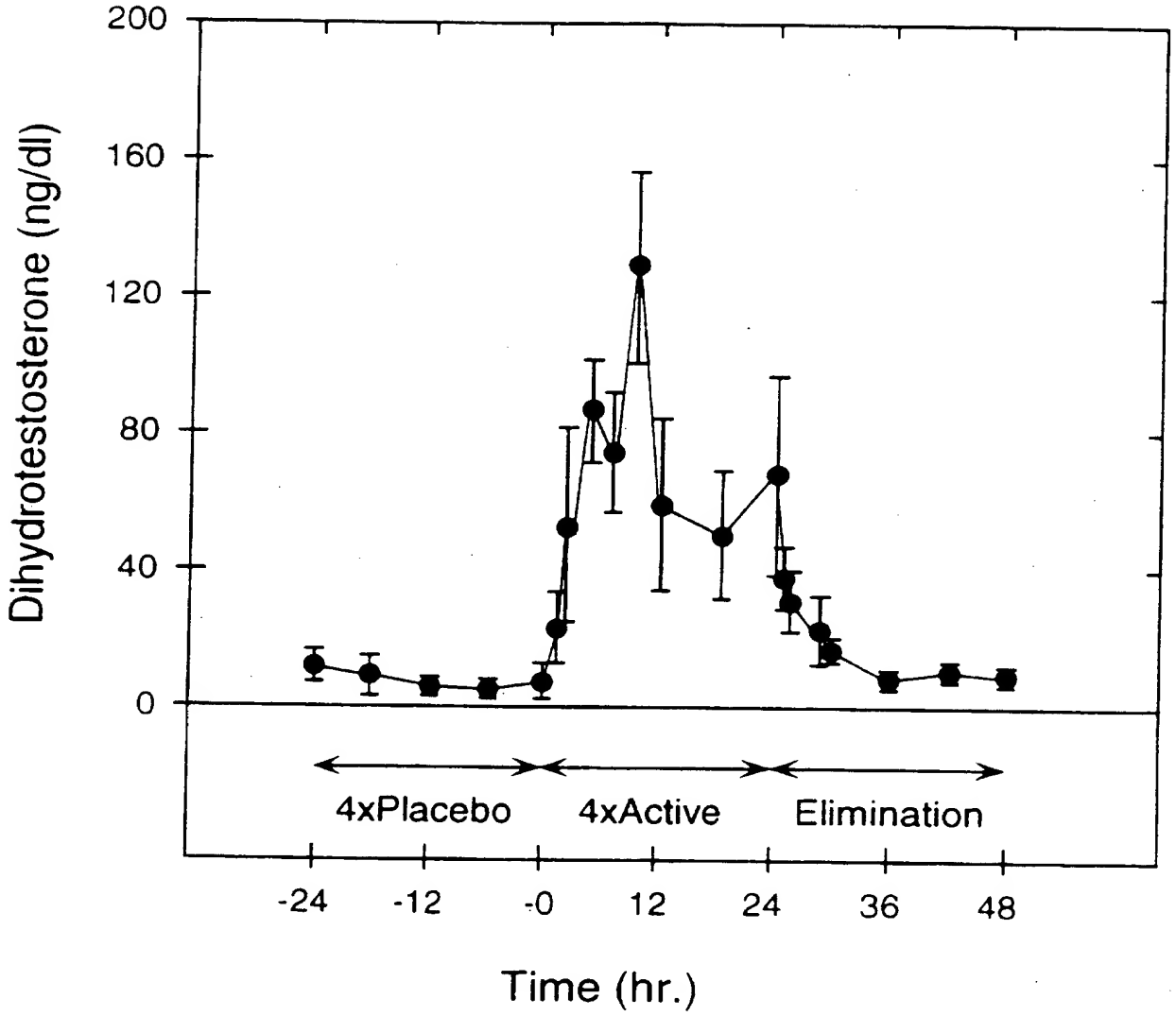

Figure 2

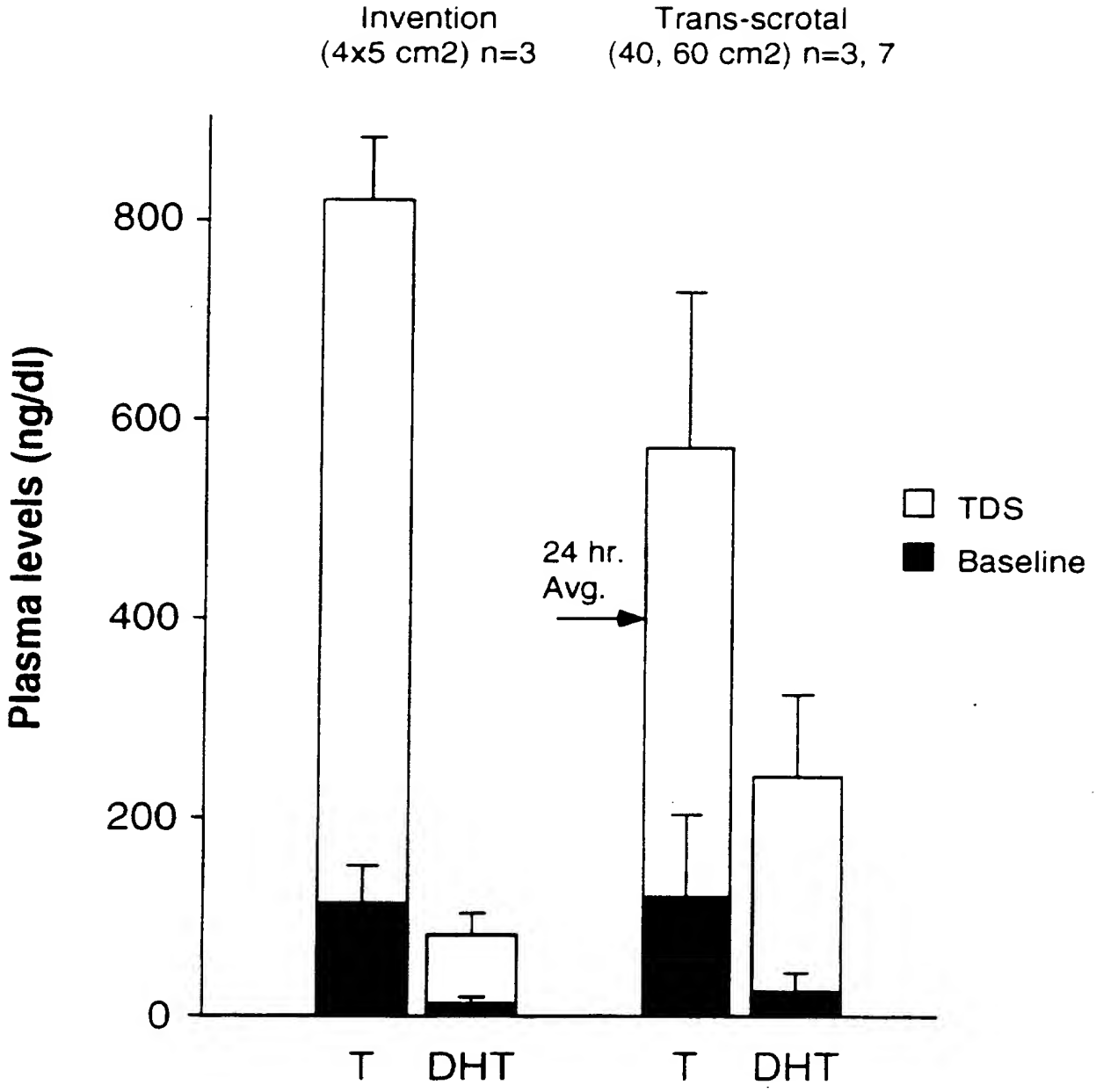

Figure 3

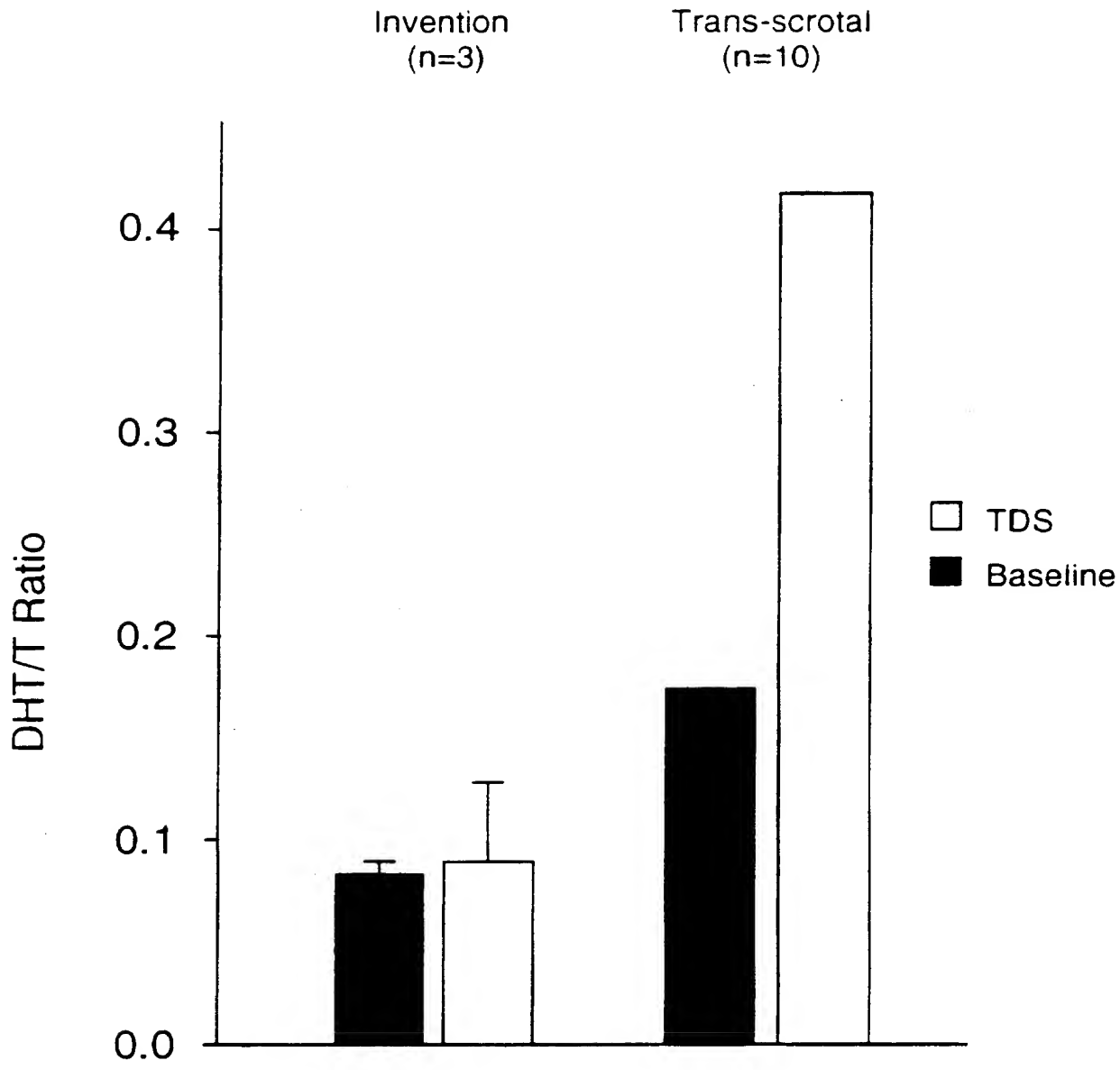

Figure 4

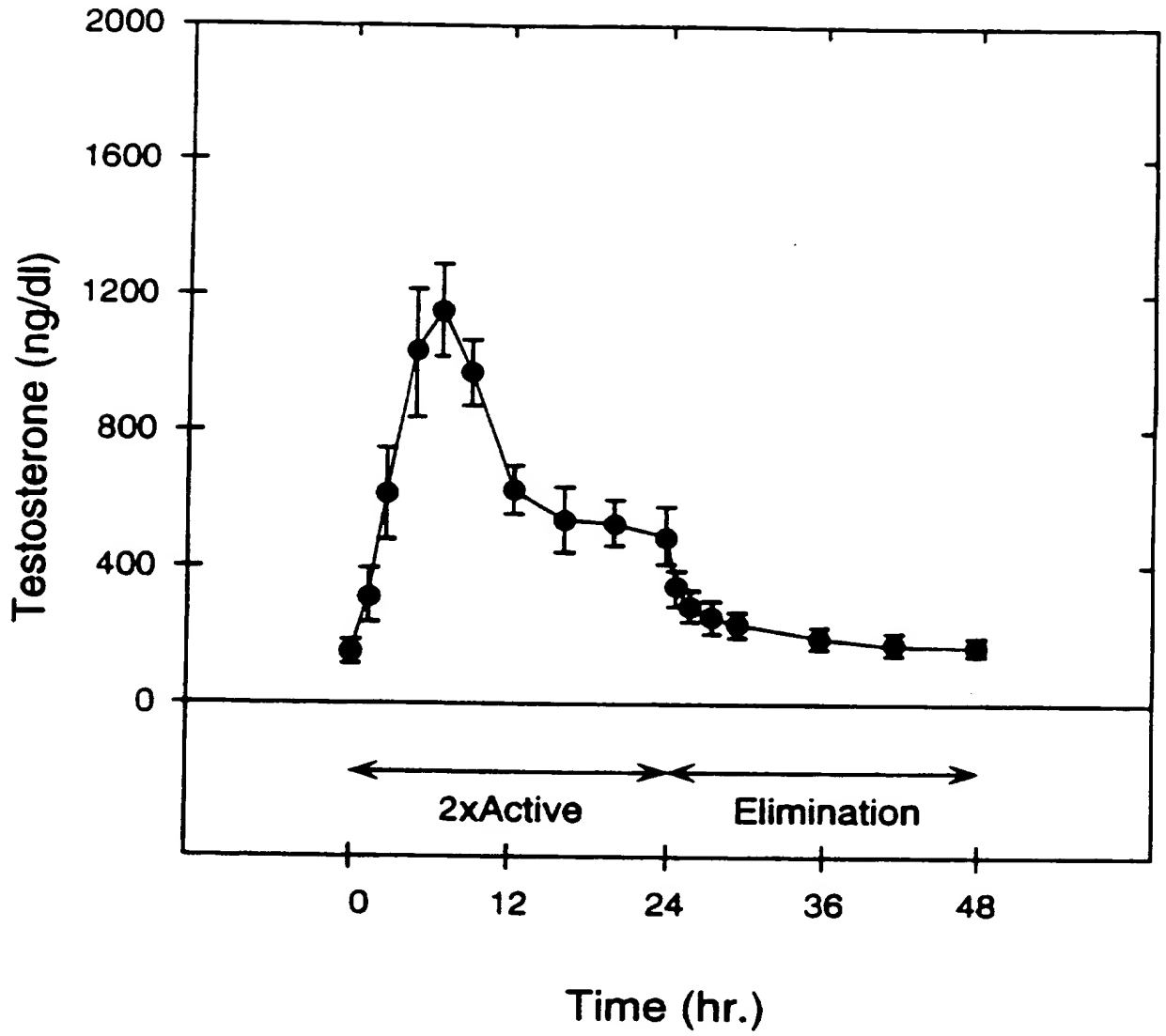

Figure 5

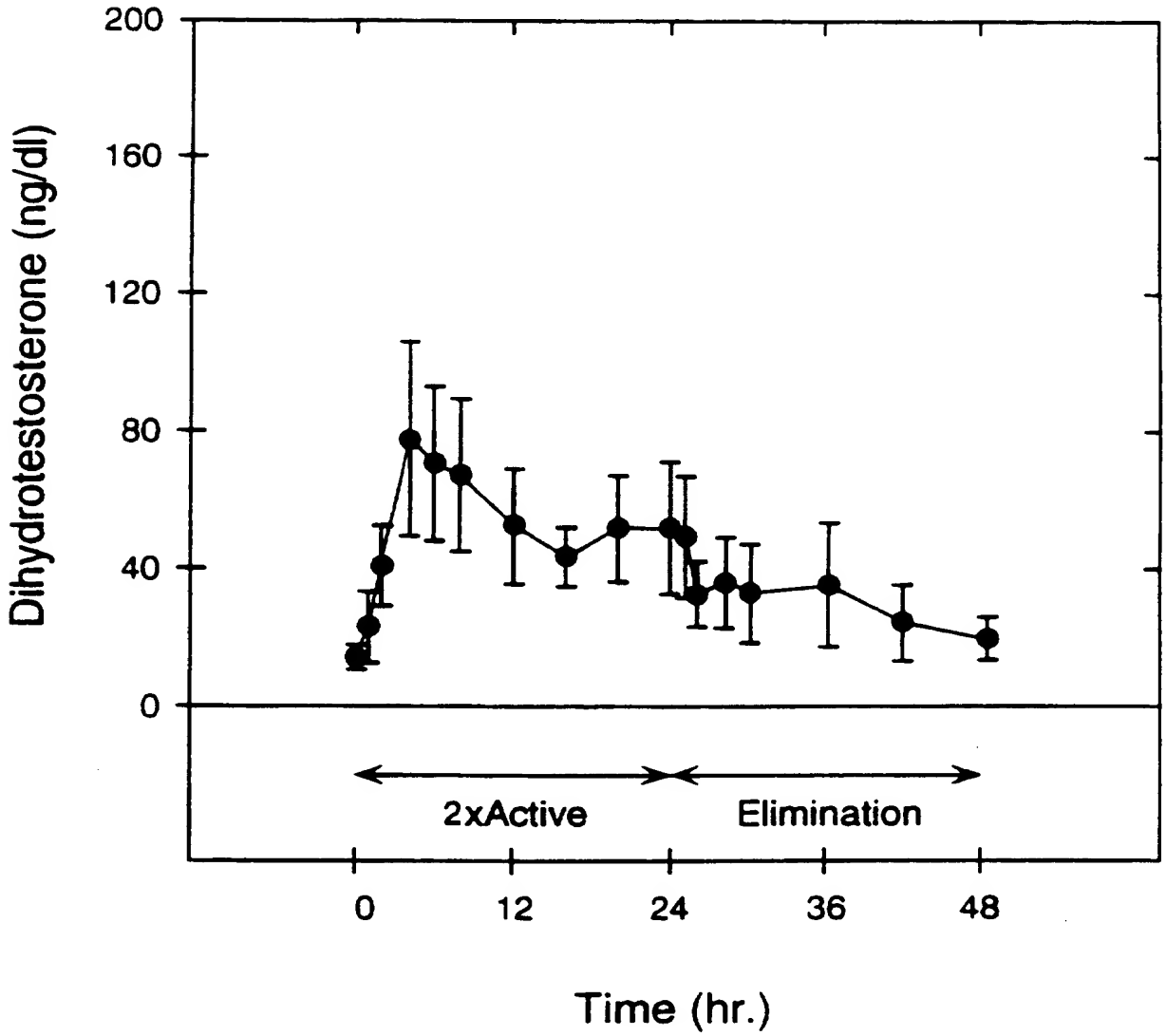

Figure 6

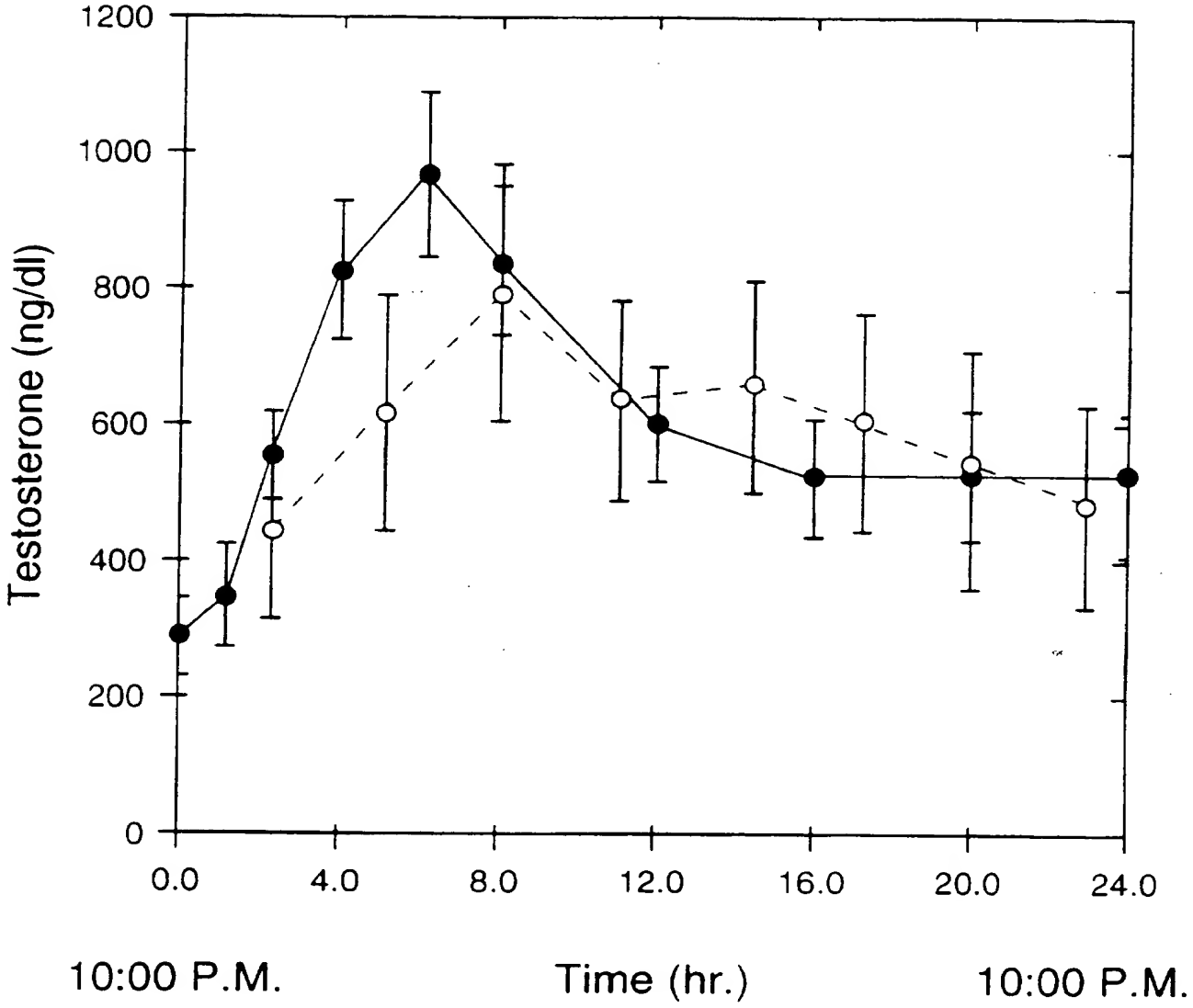

Figure 7

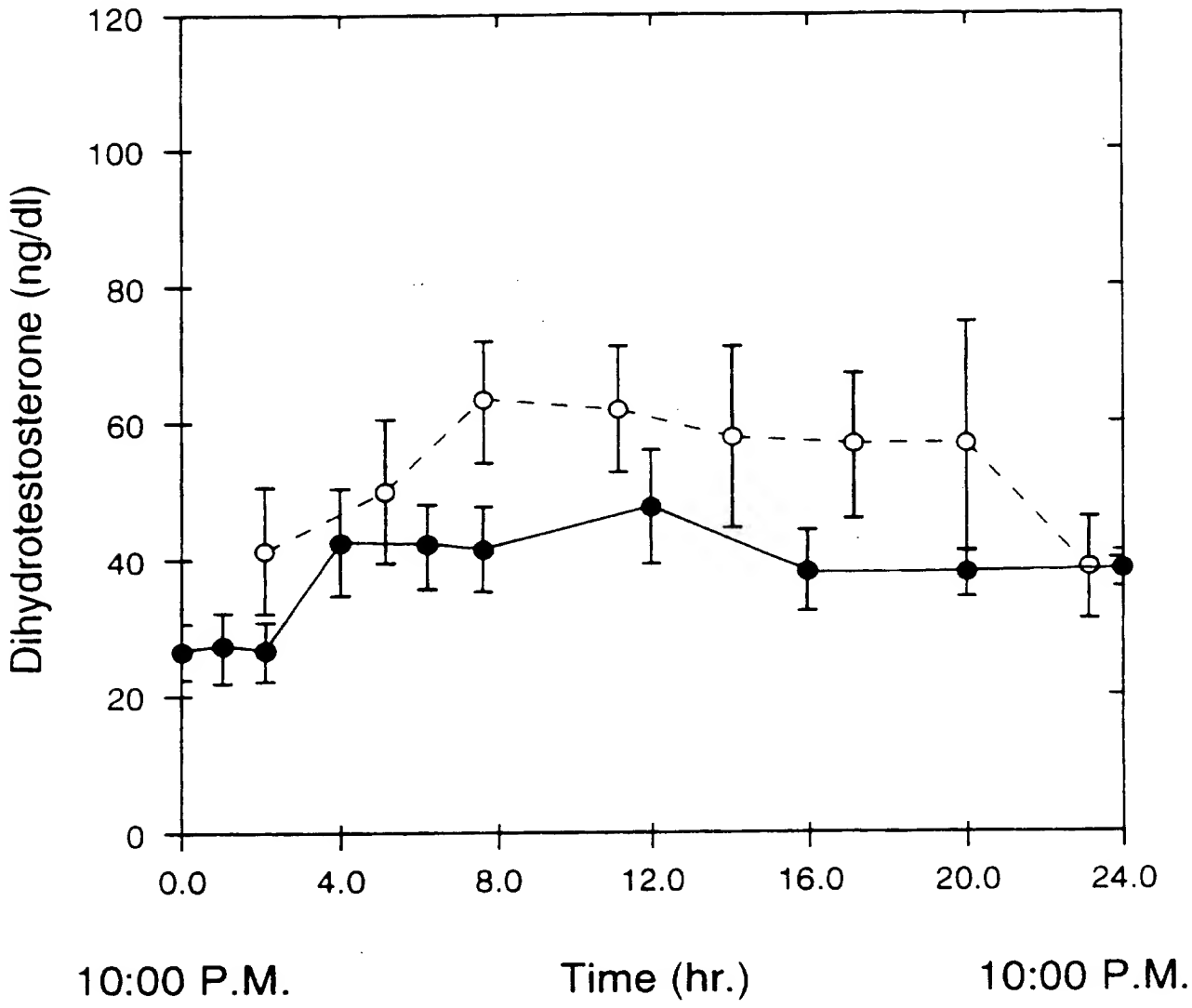

Figure 8

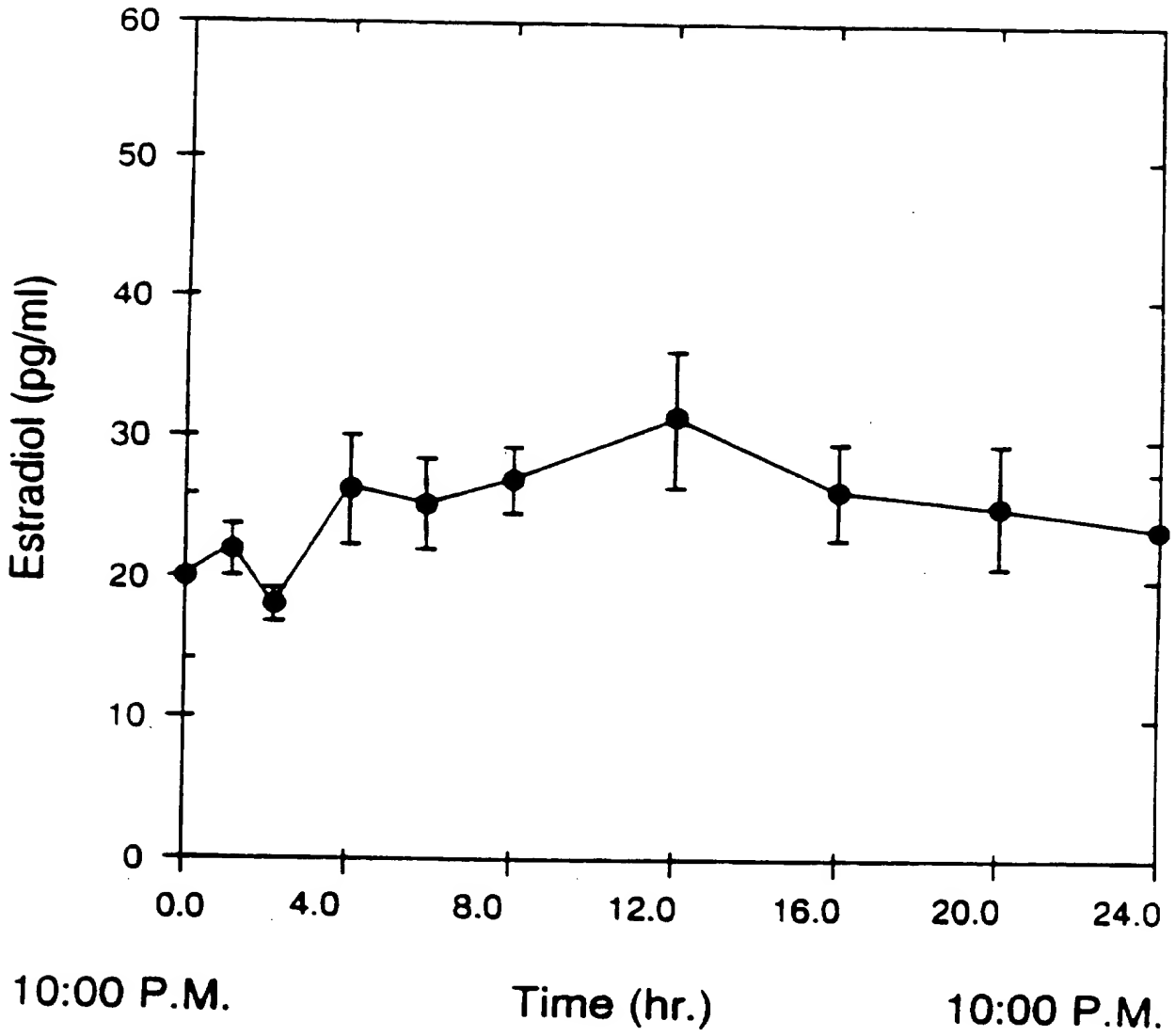

Figure 9

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91 09409

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61M 37/00

U.S. CL. 424/448

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/448, 449; 514/946, 947

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No [13]
X / Y	US, A, 4,820,720 (SANDERS ET AL) 11 APRIL 1989 See entire document.	1-3 / 11-15
X / Y	US, A, 4,855,294 (PATEL ET AL) 08 AUGUST 1989 See entire document.	1-3 / 11-18
X / Y	US, A, 4,906,463 (CLEARY ET AL) 06 MARCH 1990 See entire document.	1-3 / 11-18
Y, P	US, A, 5,059,426 (CHIANG ET AL) 22 OCTOBER 1991 See entire document.	1-3, 11-18

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09 MARCH 1992	28 APR 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Thurman K. Page

Form PCT/ISA/210 (second sheet) (Rev. 11-87)

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